

# What is the Place of ATG in Acute GVHD Prophylaxis?

James Russell

Alberta Blood and Marrow  
Transplant Program

Calgary

Canada



# ATG in acute GVHD prevention after myeloablative HSCT

- Rationale
- Potential risks and benefits
- Evidence for effect of ATG in MRD/UD SCT
  - comparative studies of
    - Incidence of aGVHD
    - GVHD related mortality
  - Relationship of aGVHD to antibody levels
  - Dose and timing
- Challenges:
  - Relapse
  - High risk patients
  - Progressive cGVHD

# Commonly used ATG preparations

<b>Preparation</b>	<b>Source</b>	<b>Immunogen</b>
Atgam	Horse	Human lymphocytes
Fresenius	Rabbit	Cell line
Lymphoglobulin	Horse	Human thymocytes
Thymoglobulin	Rabbit	Human thymocytes

# ATG in Stem Cell Transplant

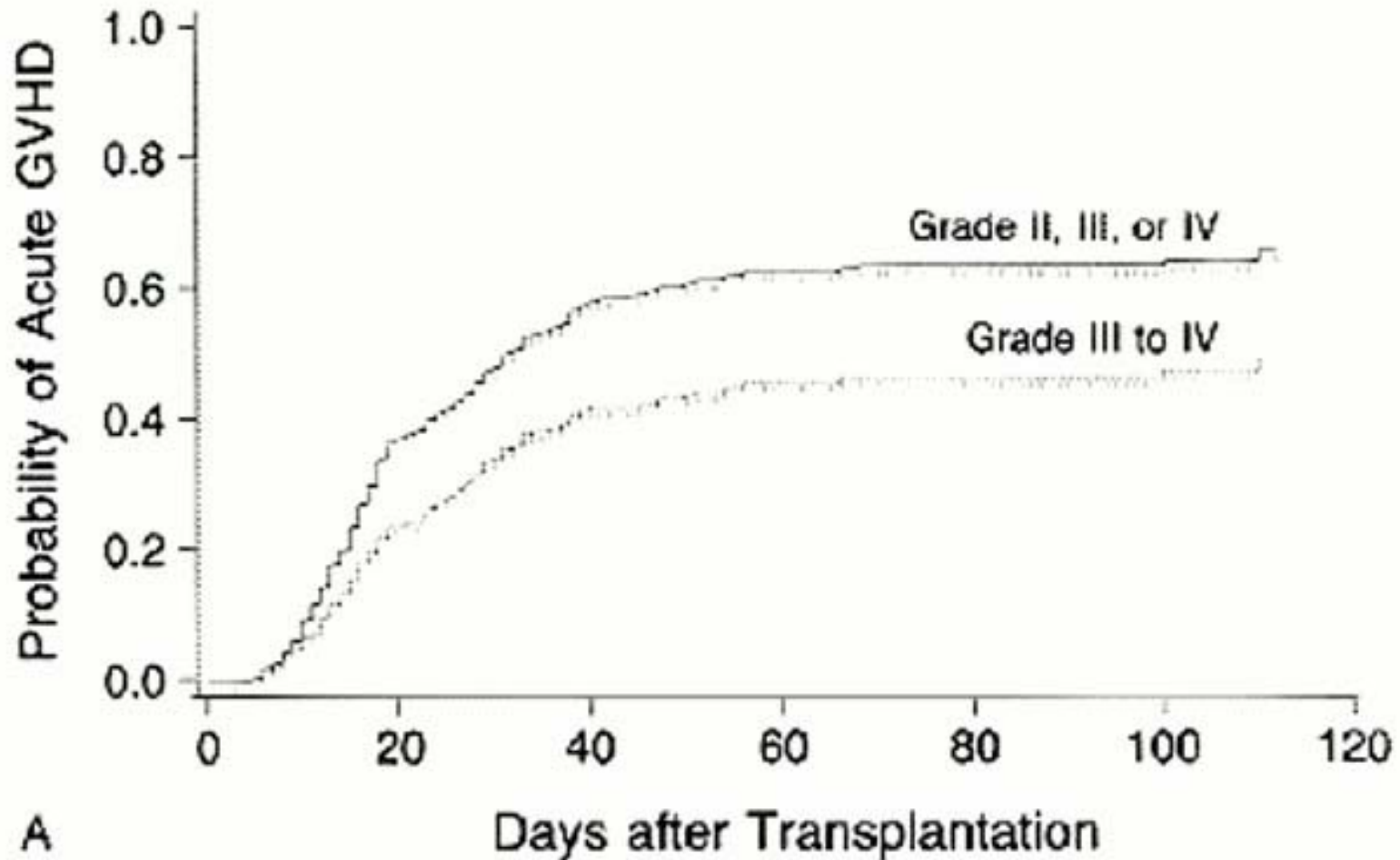
- Potential advantages
  - less GVHD

- Potential disadvantages
  - more relapse
  - more infection
  - PTLPD

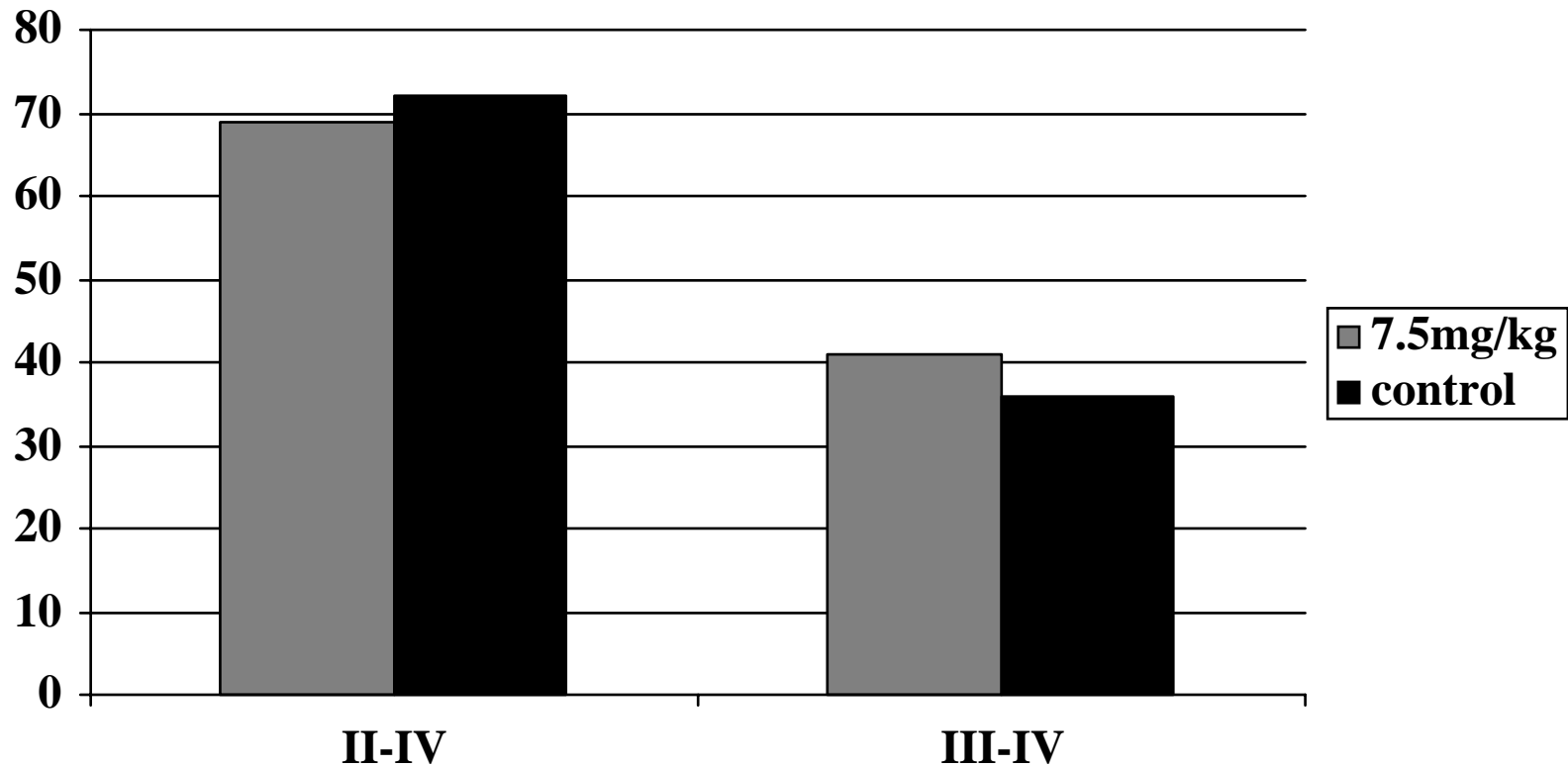
Acute GVHD Grade III-IV  
occurs in 25-50% of unrelated  
donor HSCT with Mtx/CSA  
prophylaxis

Is this reduced by ATG?

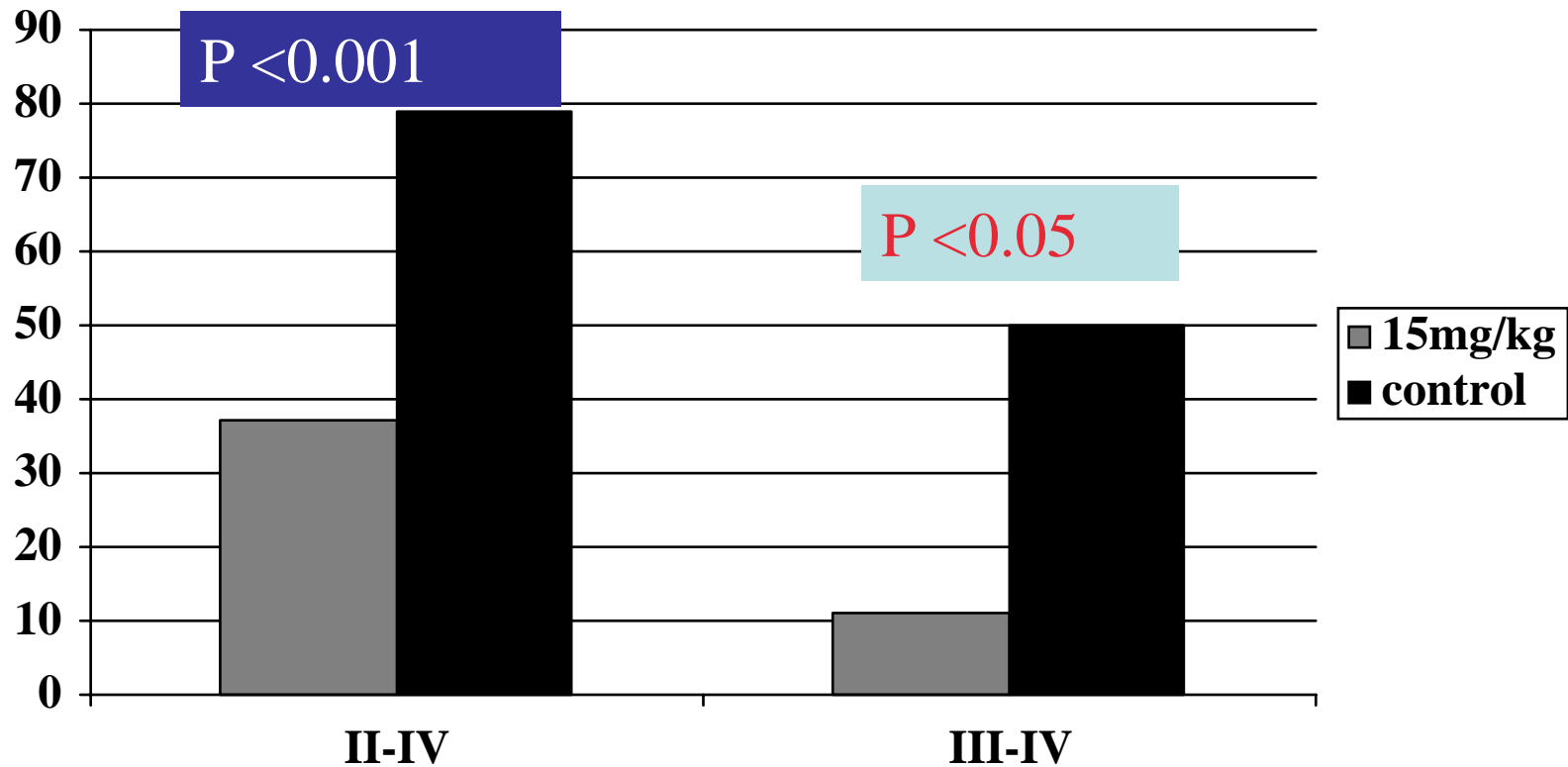
# Acute GVHD after unrelated donor bone marrow transplantation



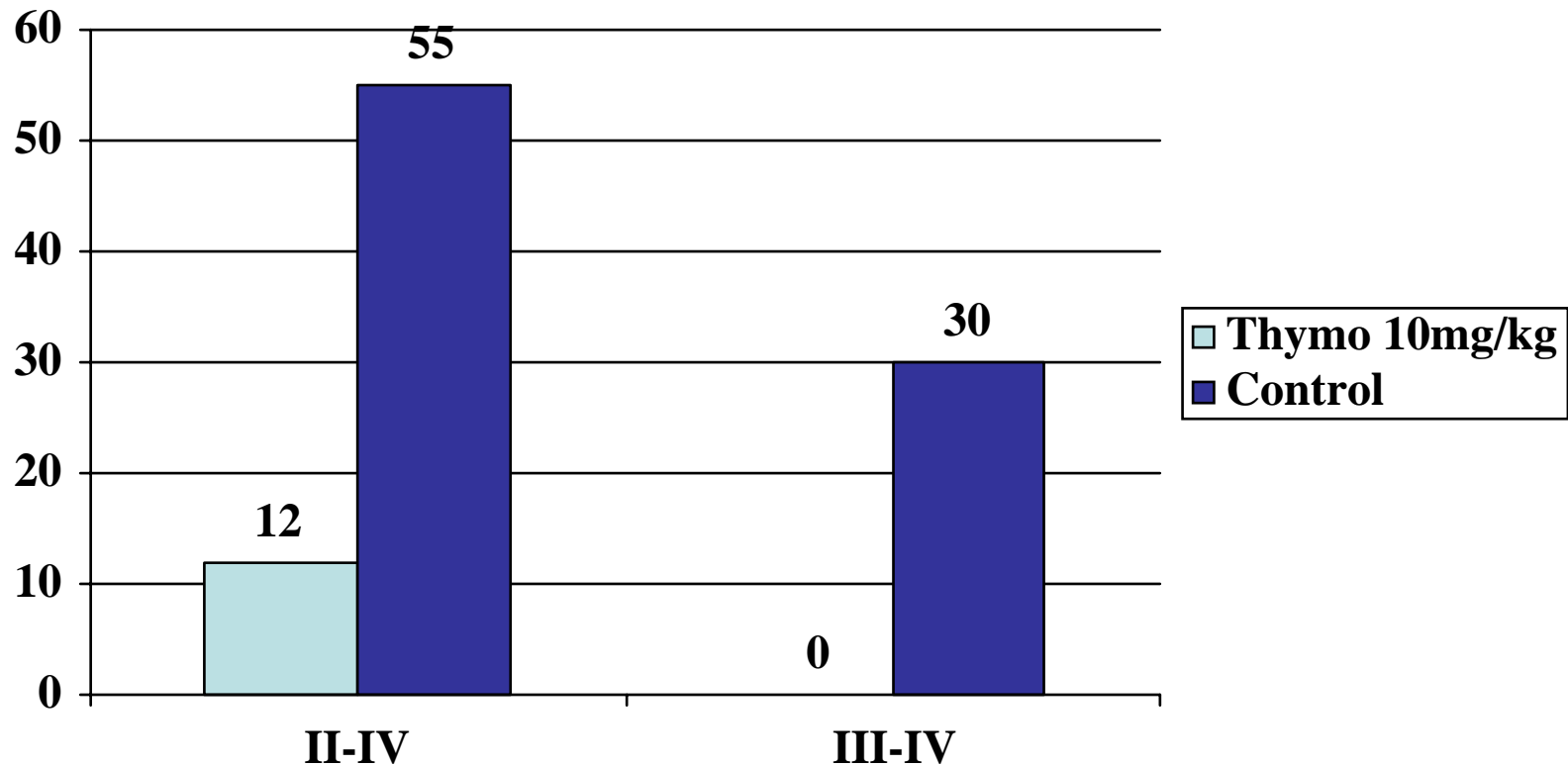
# Thymoglobulin and Acute GVHD Unrelated Donors Bone marrow



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Remberger et al. BMT 2002. Retrospective, two centre

# Changes in allo SCT protocols 1993-2004

BCT

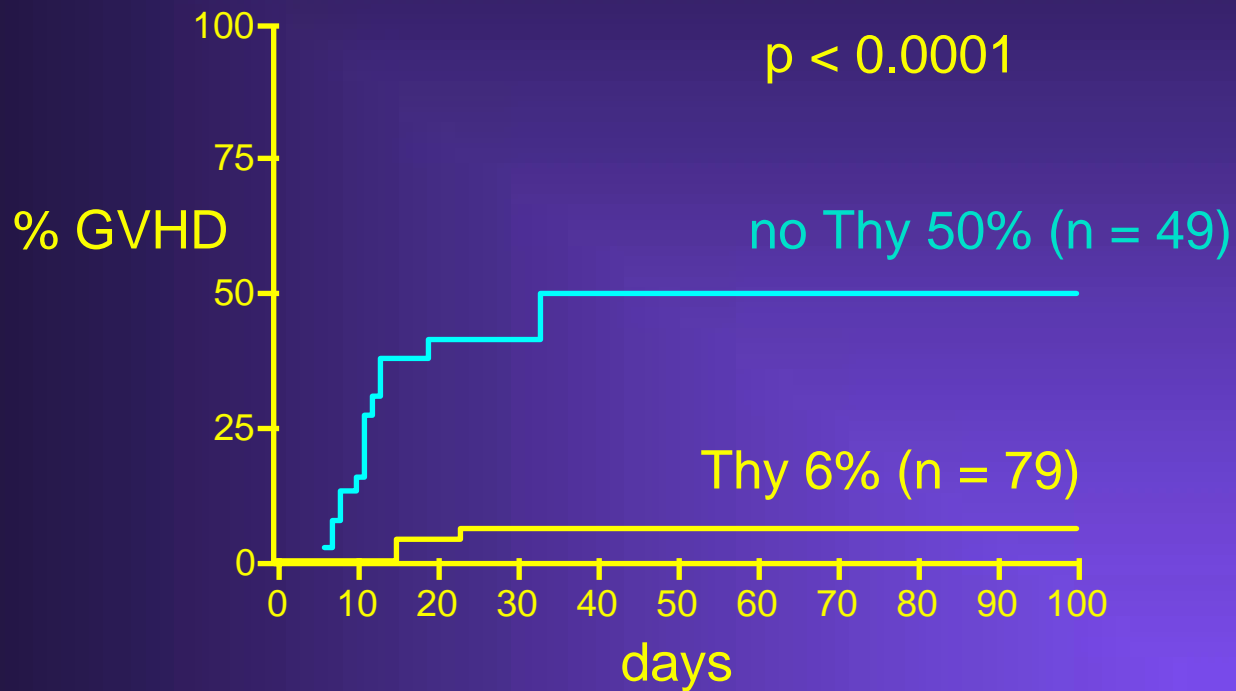
Thymoglobulin  
in UD



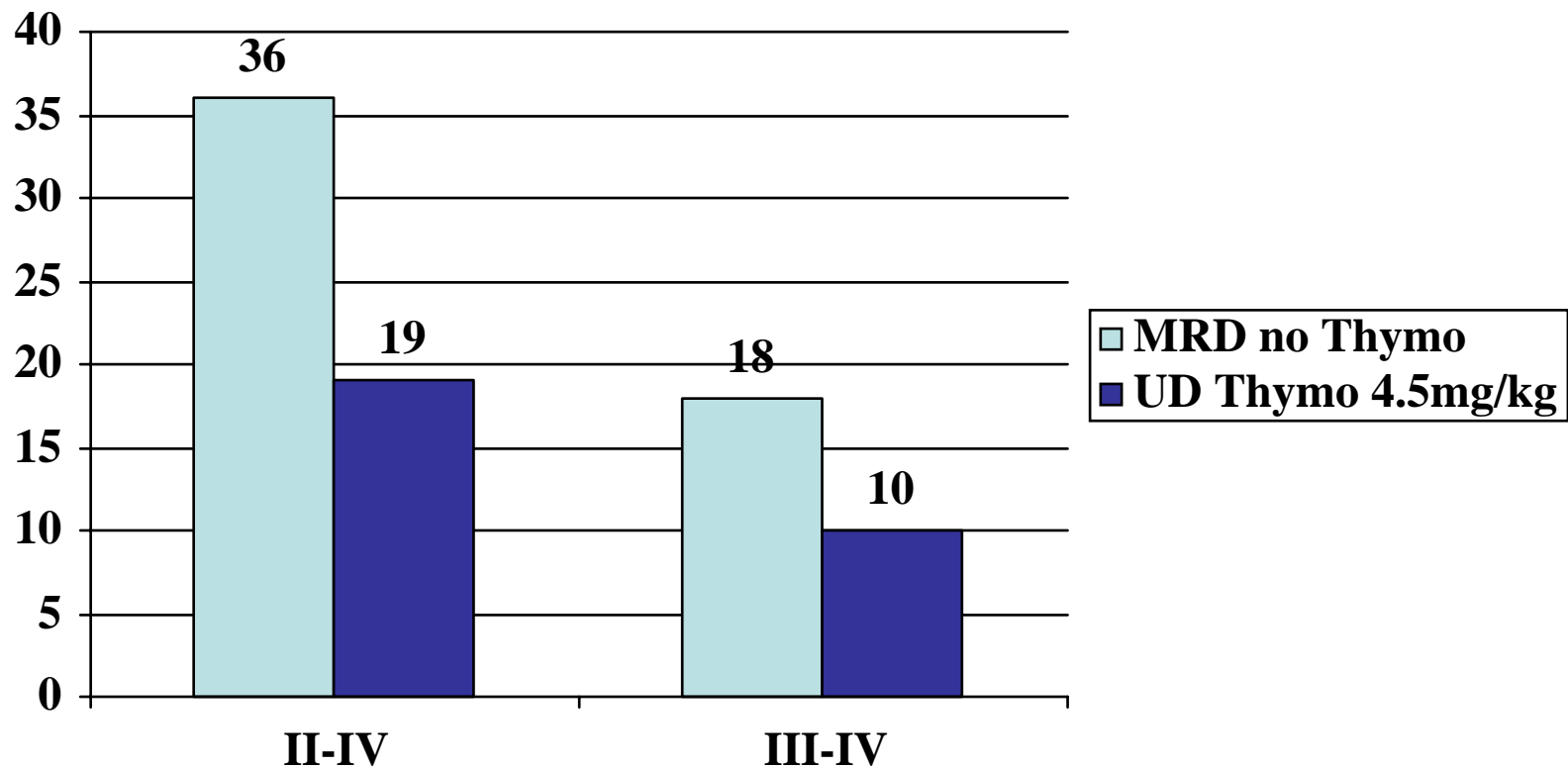
# Grade III-IV acute GVHD

## Unrelated donors

### Bone Marrow

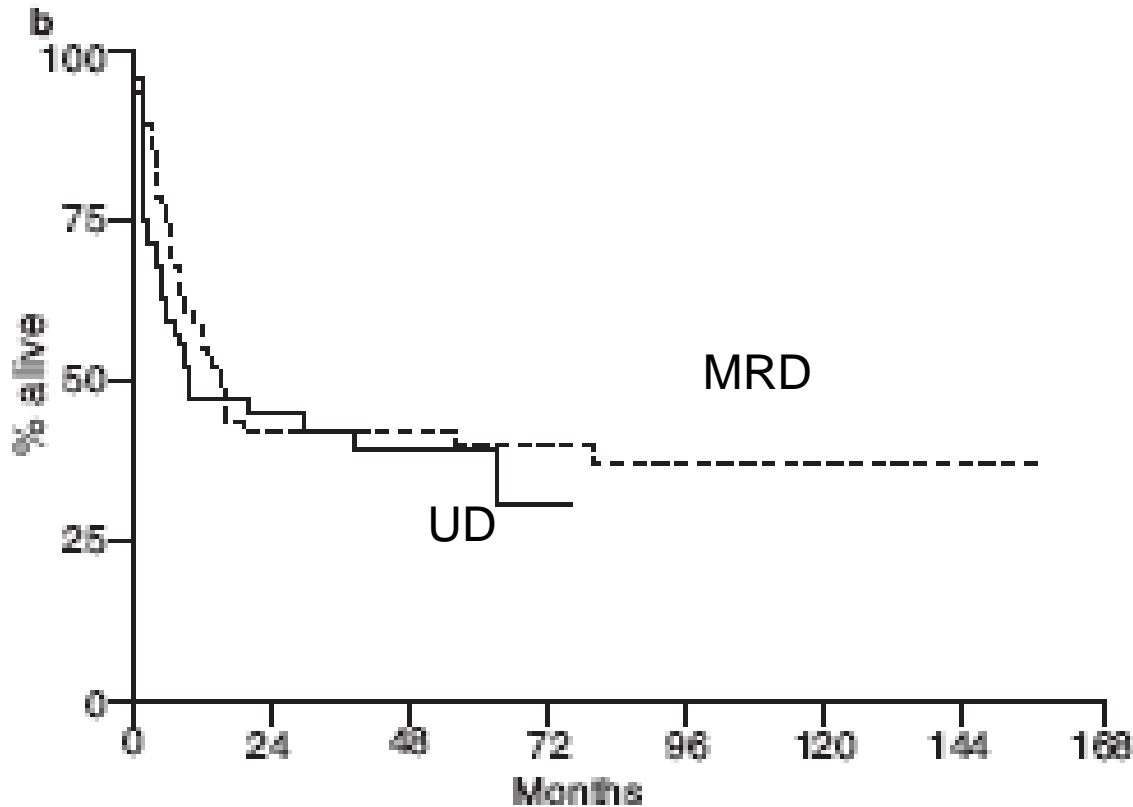


# Acute GVHD-RD/UD Bone Marrow Transplants



Duggan et al. BMT 2002. Retrospective, matched pair, single centre

# Matched pair analysis of UD BMT with Thymoglobulin vs MRD BMT



Similar:  
OS  
DFS  
Relapse  
TRM

# Studies of ATG in GVHD prevention

QuickTime™ and a  
decompressor

# Studies of ATG in GVHD prevention

are needed to see this picture.

"....none of the numerous retrospective studies\_reports decreased survival in patients receiving ATG."

Bacigalupo. BMT 2005

Randomized study  
Unrelated donors  
ATG Fresenius  
Mostly Blood cells

Finke et al. Lancet Oncol 2009

# Acute GVHD II-IV Unrelated donors ATG Fresenius

P = 0.01

QuickTime™ and a  
decompressor  
are needed to see this picture.

# Acute GVHD III-IV

## Unrelated donors

### ATG Fresenius

QuickTime™ and a  
decompressor  
are needed to see this picture.

# Survival Unrelated donors ATG Fresenius

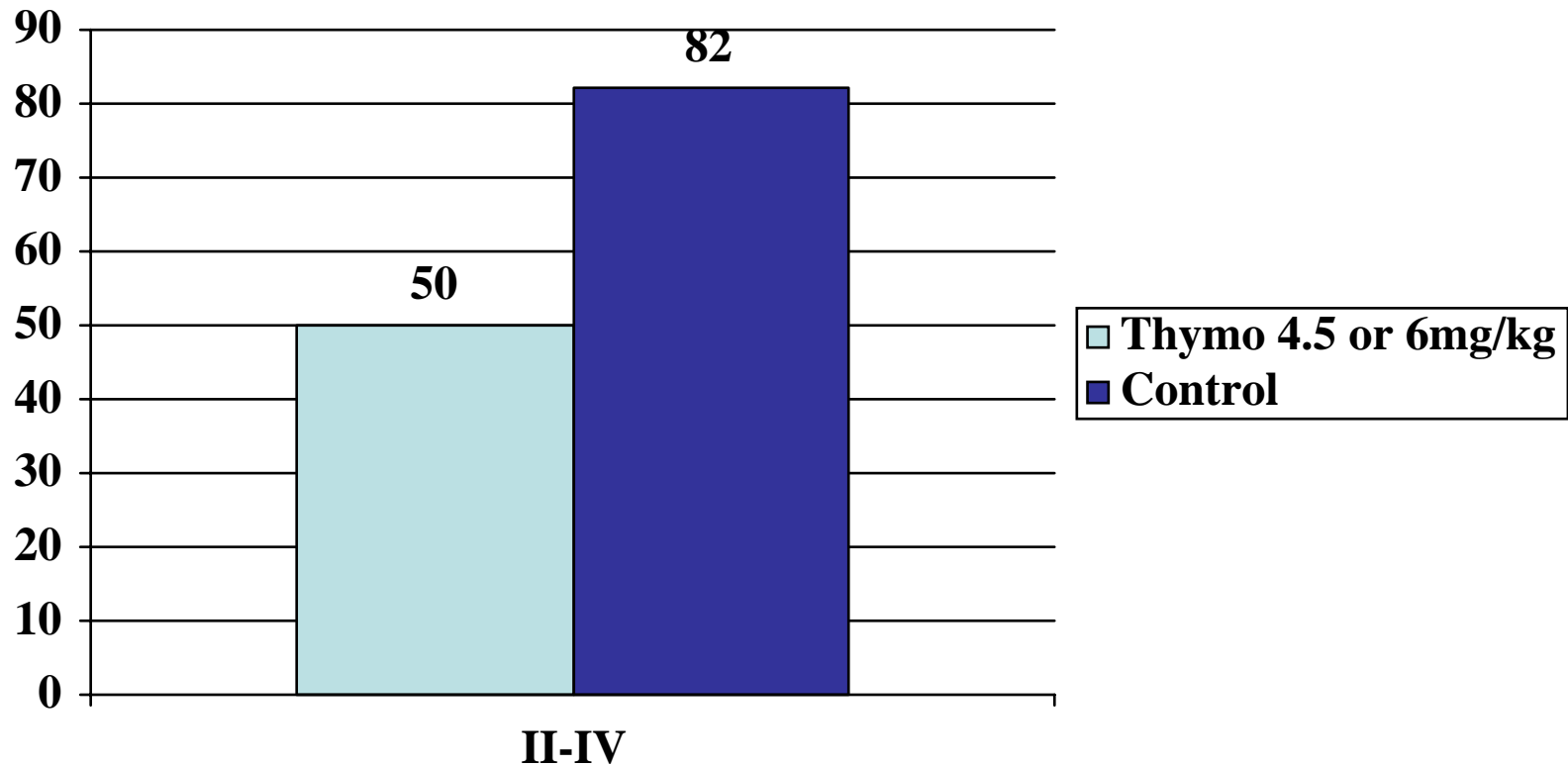
ATG

QuickTime™ and a  
decompressor  
are needed to see this picture.

Control

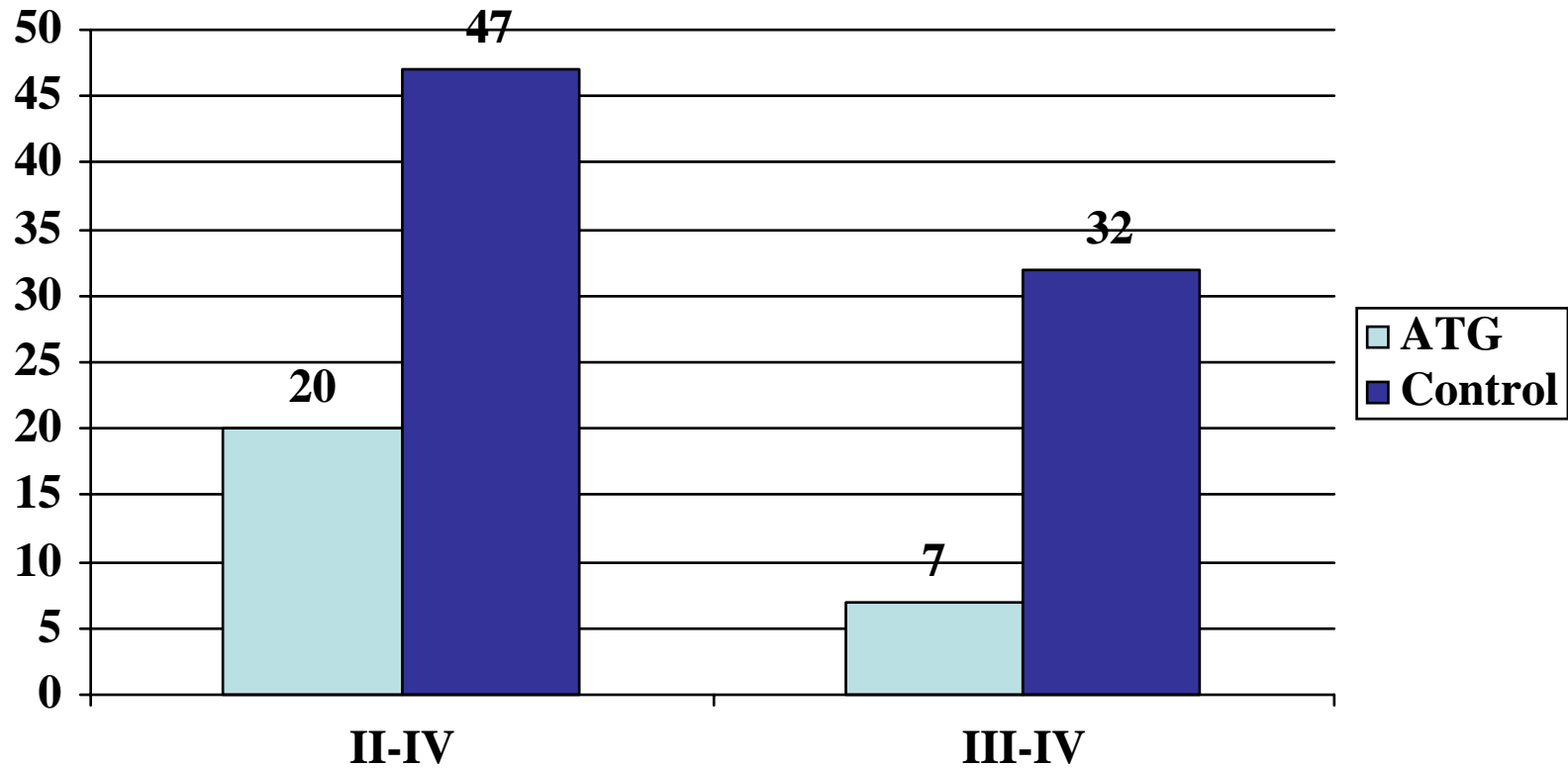
# ATG in matched related donor transplants

# Acute GVHD-RD/UD Blood cell transplants



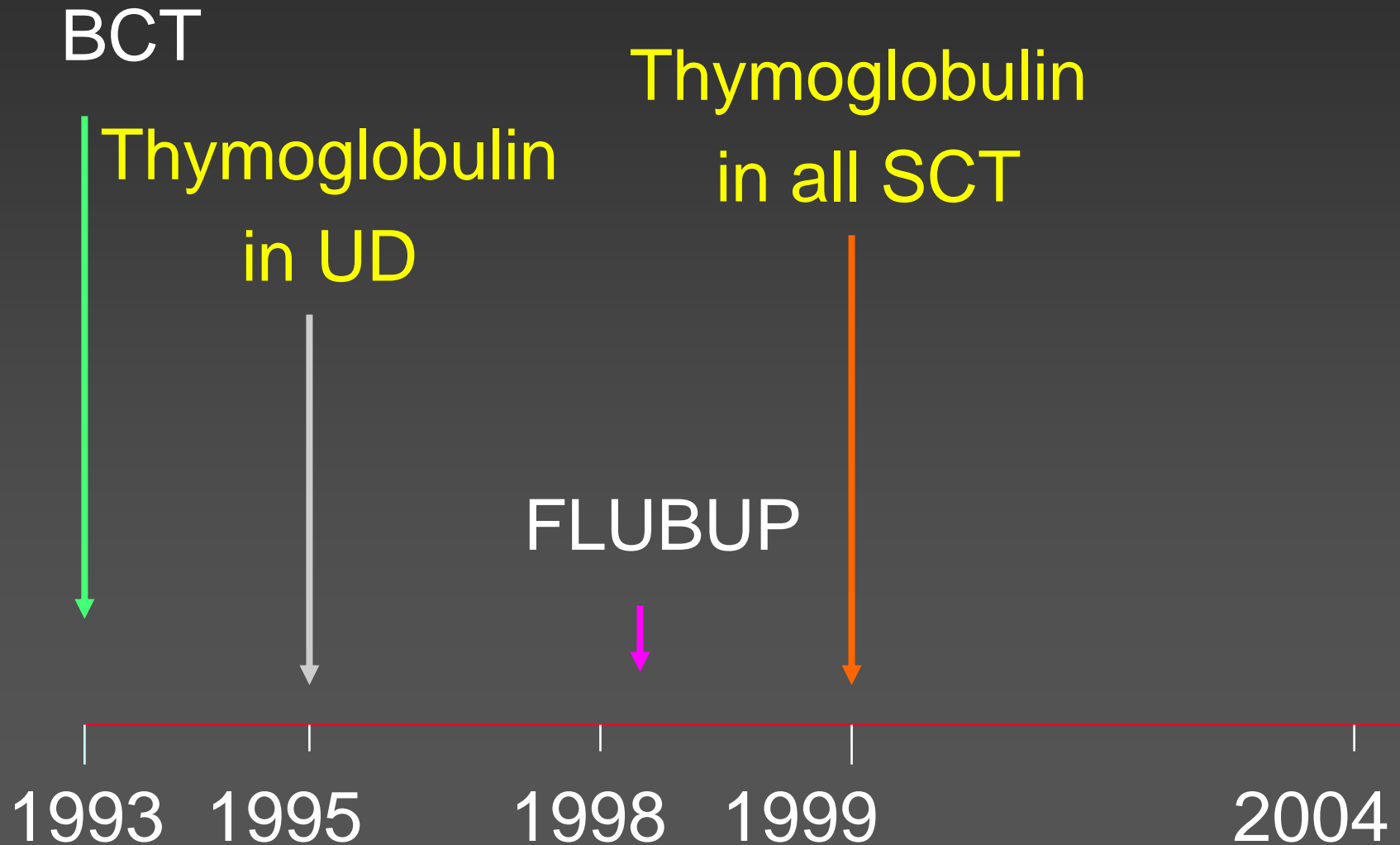
Deeg et al. BBMT Retrospective, single centre

# Acute GVHD - Related Donors\*



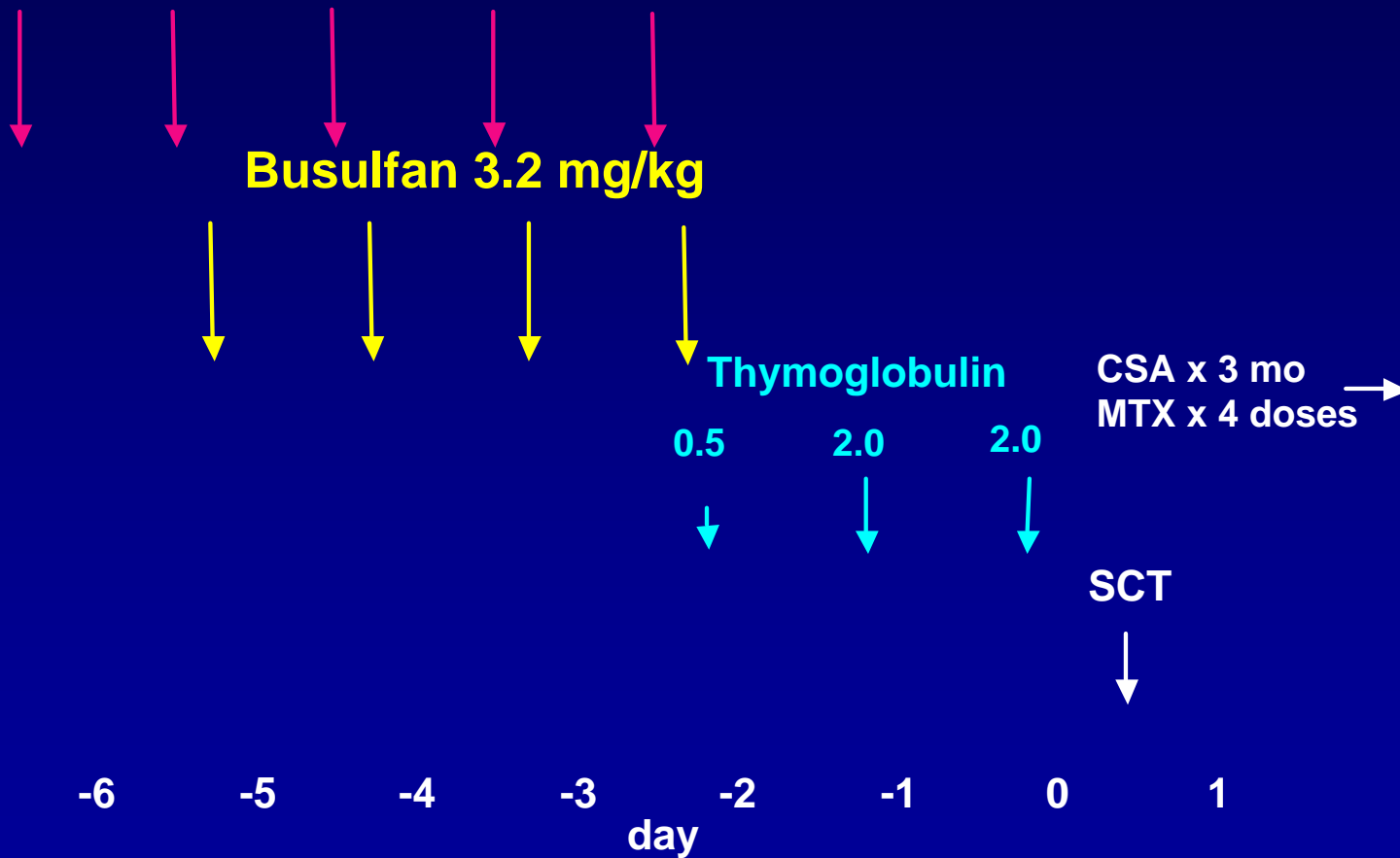
Kroger et al. BMT 2002 Retrospective, good risk CML & AML,  
ATG Fresenius  
\*mostly BMT

# Changes in allo SCT protocols 1993-2004

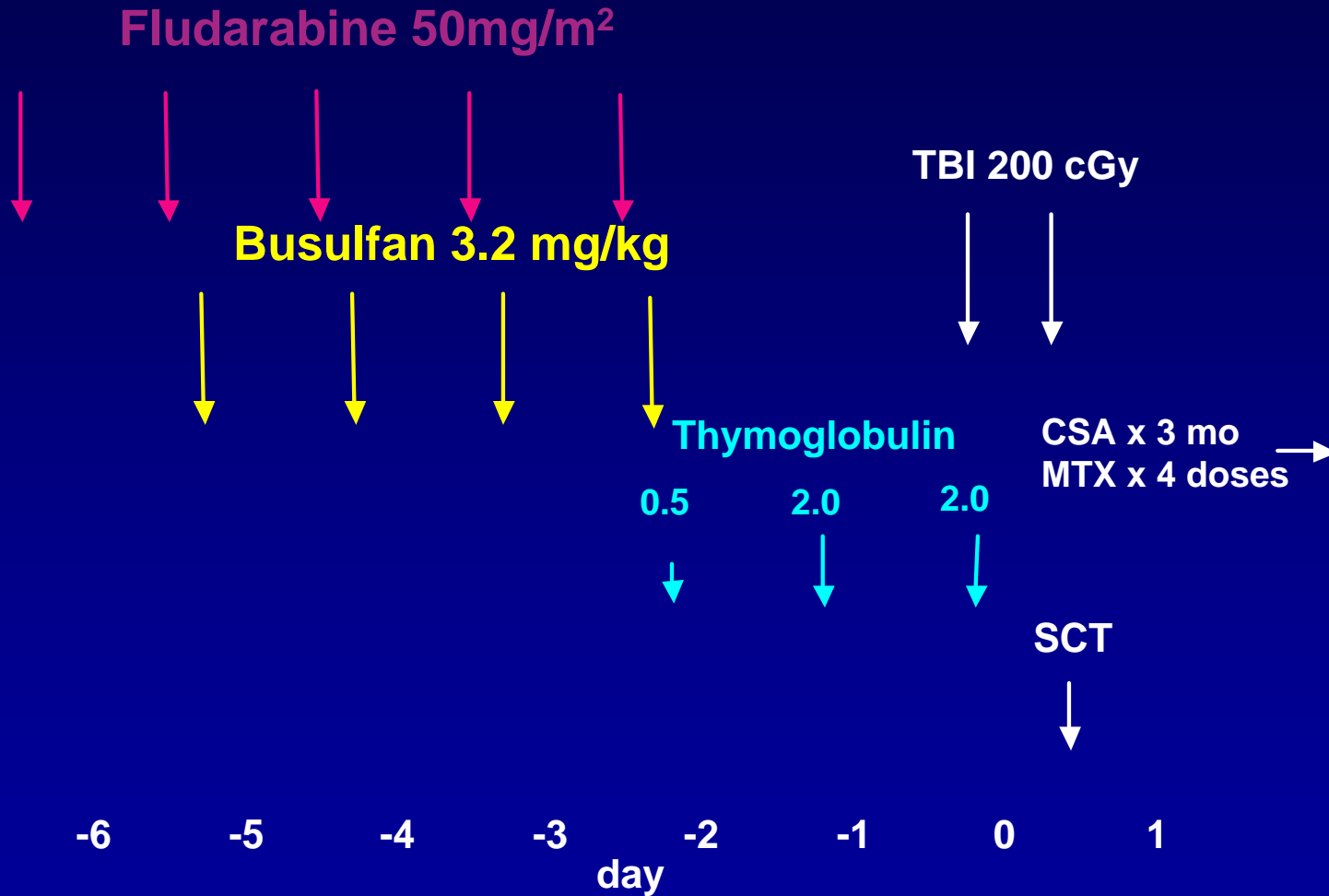


# FLUBUP/Thymo/regimen

Fludarabine 50mg/m<sup>2</sup>



# FLUBUP/Thymo/TBI regimen



# Thymoglobulin dosing

- Total dose 4.5 mg/kg over 3 days (6mg/kg if <30kg)



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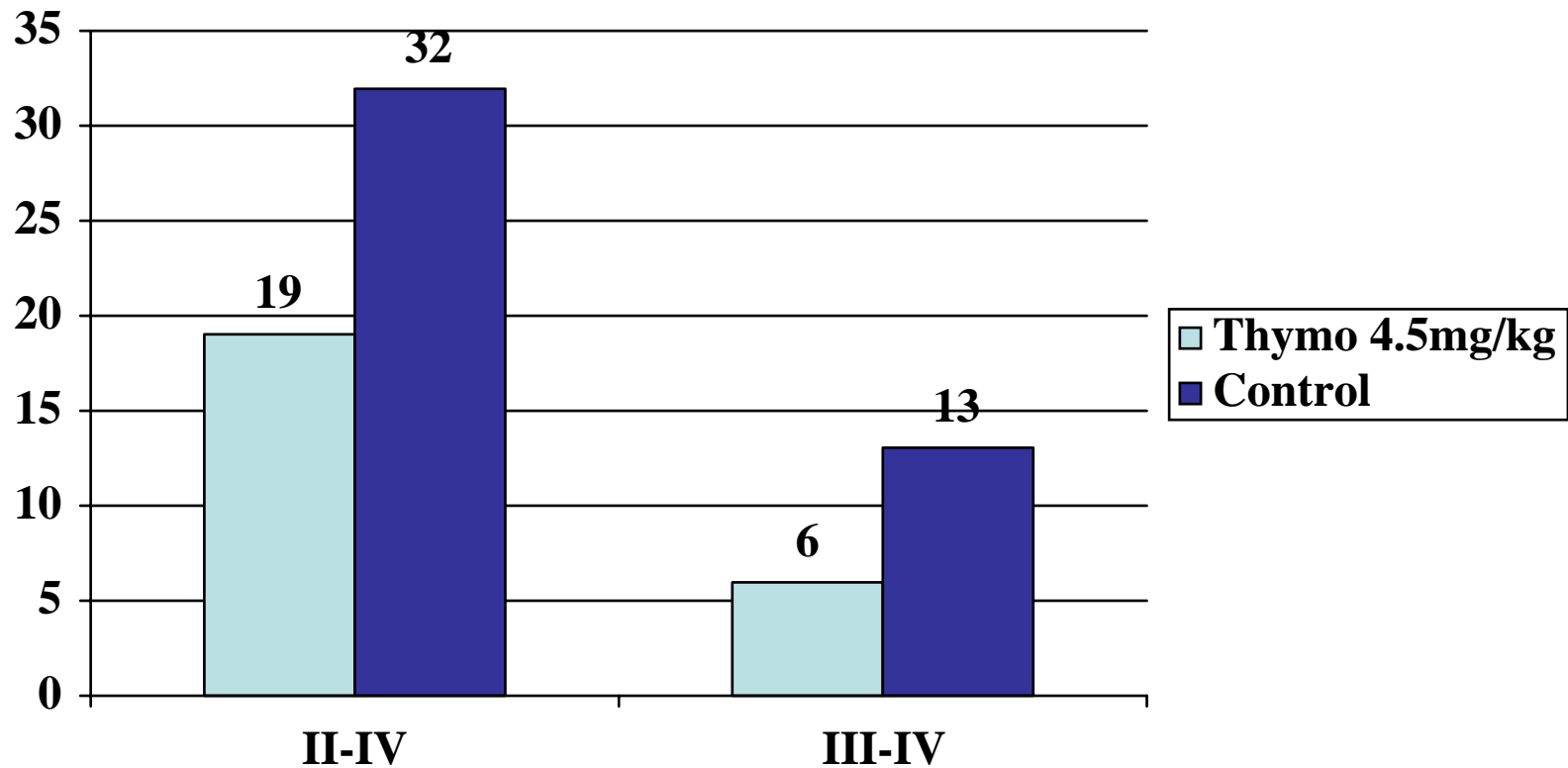
- Total dose 4.5 mg/kg over 3 days (6mg/kg if <30kg)
- 0.5 mg/kg as first dose may improve tolerability
- **Completed day 0**



# Matched pair analysis of MRD BCT

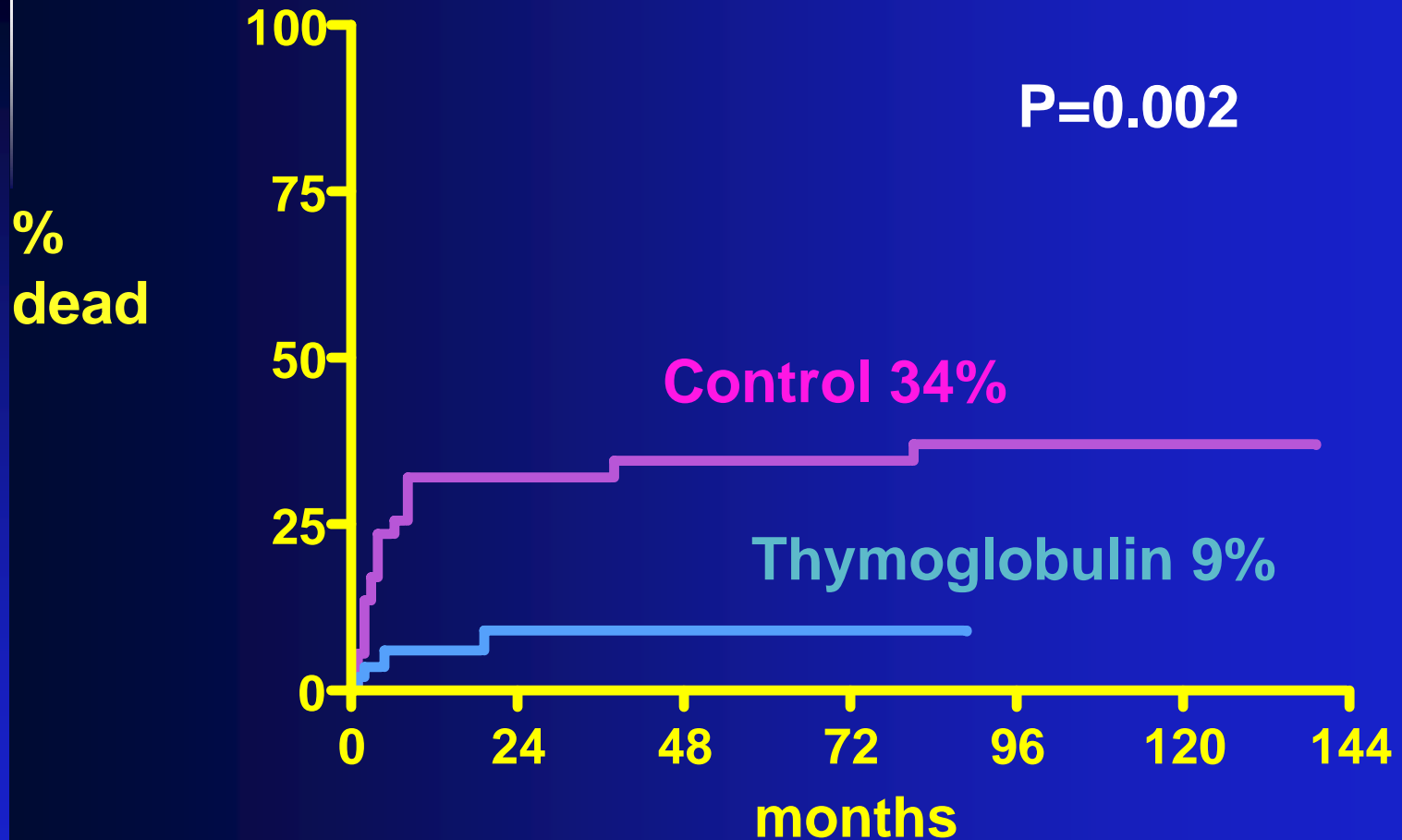


# Acute GVHD-Related Donors Blood cells



Russell et al. BBMT 2007. Retrospective, matched pair

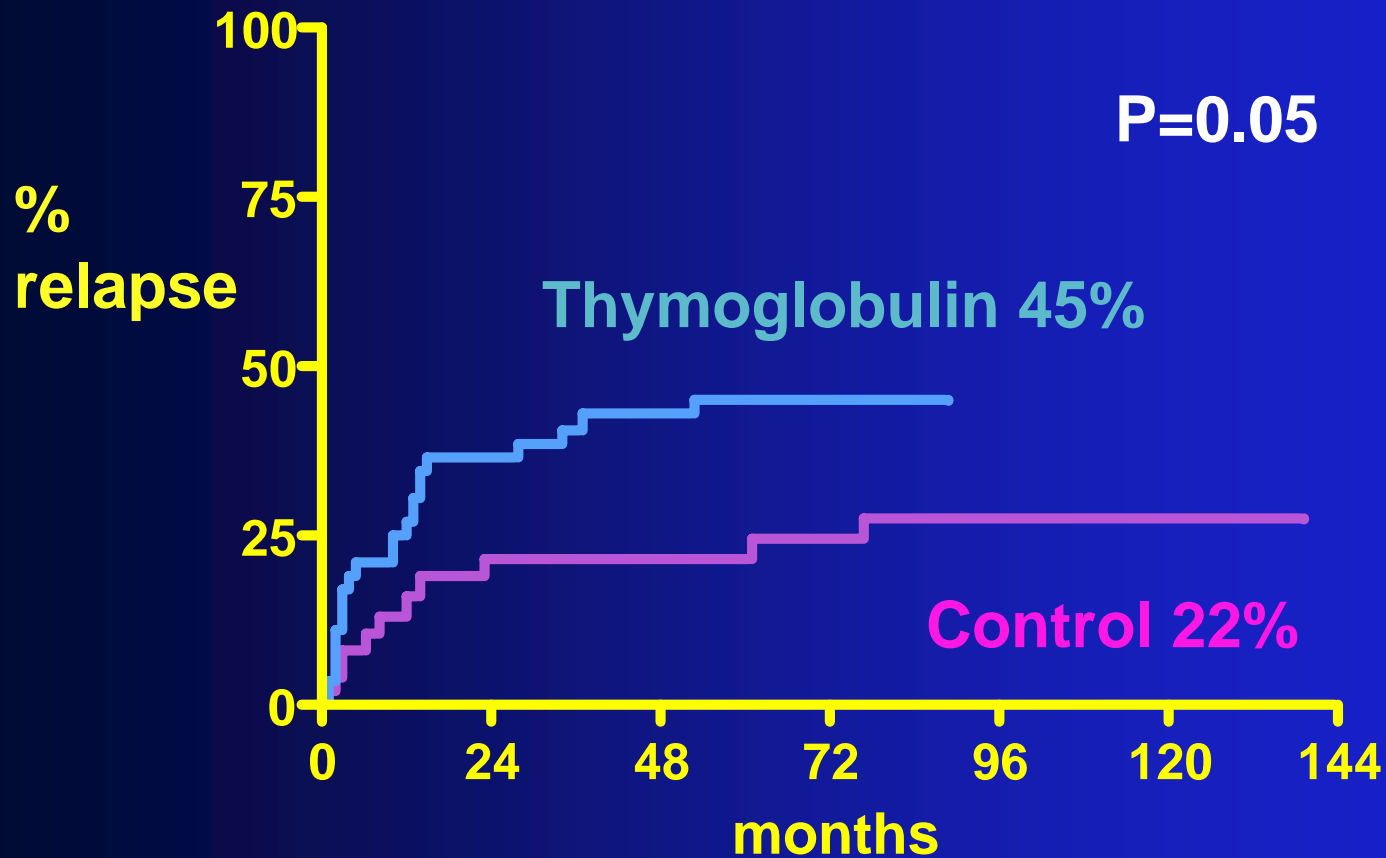
# Transplant-related mortality (5yr)



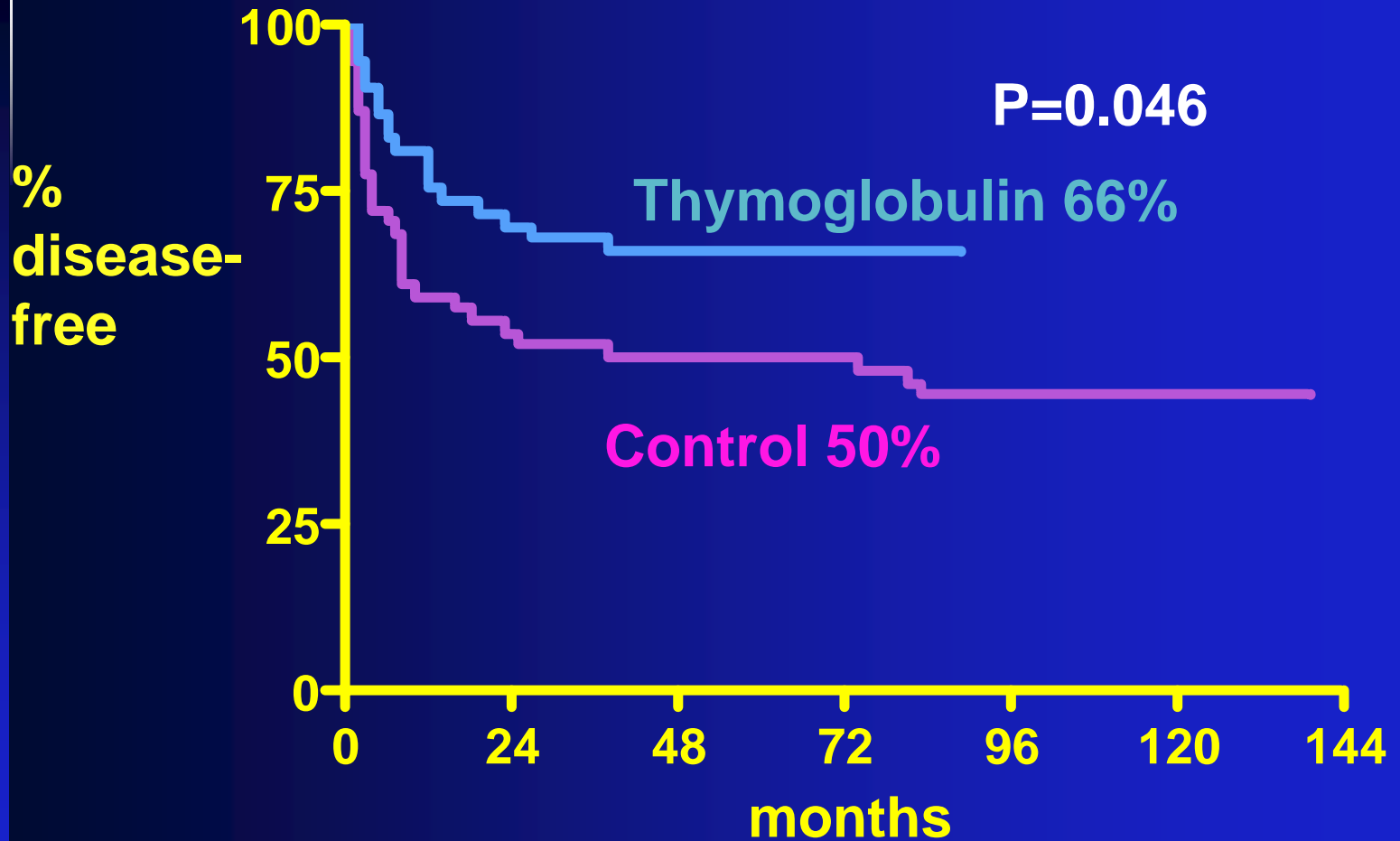
# Matched pair analysis (n=54)

**GVHD related death** - 3 in Thymoglobulin group vs 14 in controls (p=0.007)

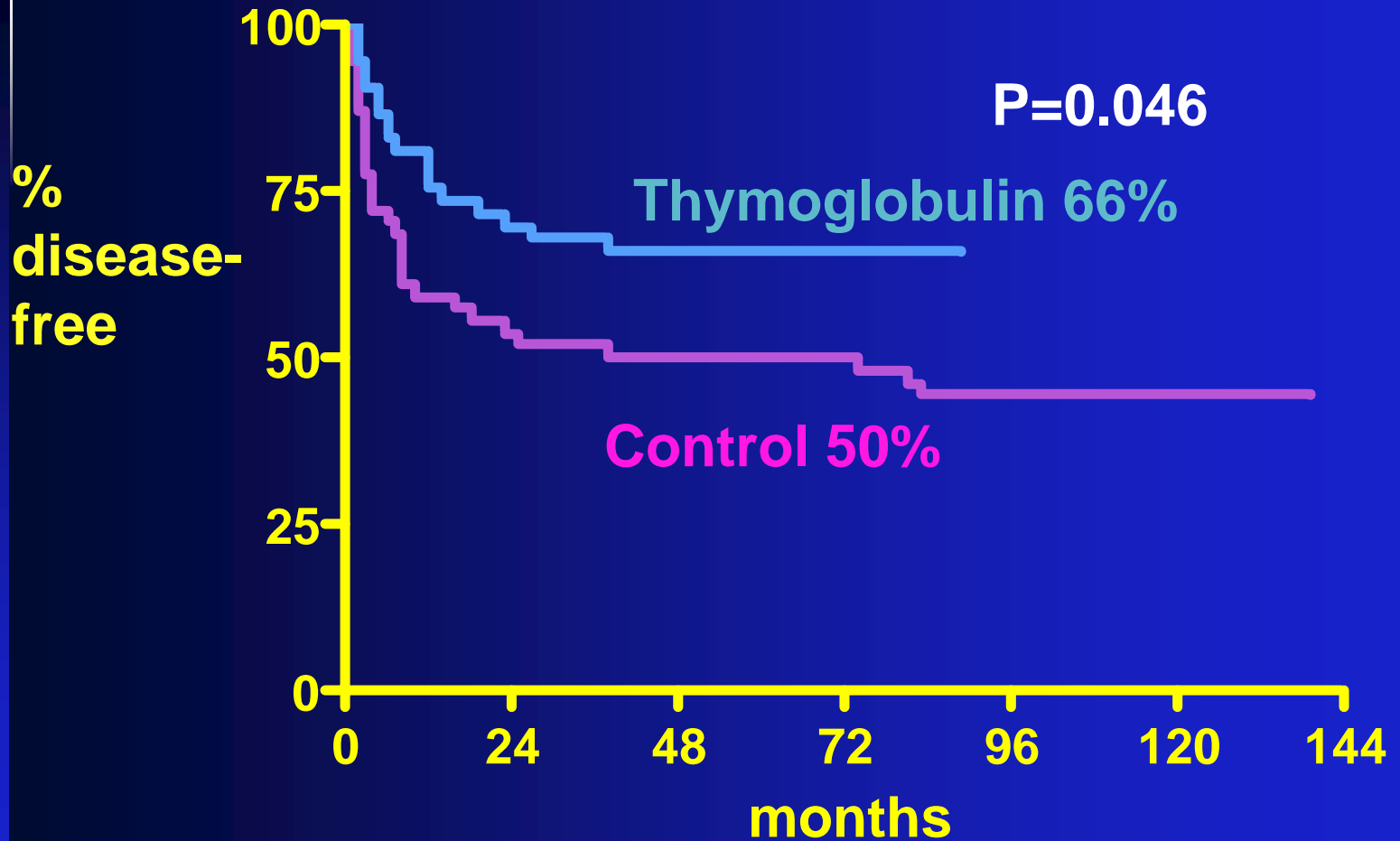
# Relapse (5yr)



# Survival (5yr)



# Survival (5yr)



# Case-control study with CIBMTR



# Case-control study with CIBMTR

<b>Risk</b>	<b>RR Case vs control</b>	<b>p</b>
Acute GVHD II-IV	0.34	0.0001
Overall mortality	0.48	0.003

# Case-control study with CIBMTR

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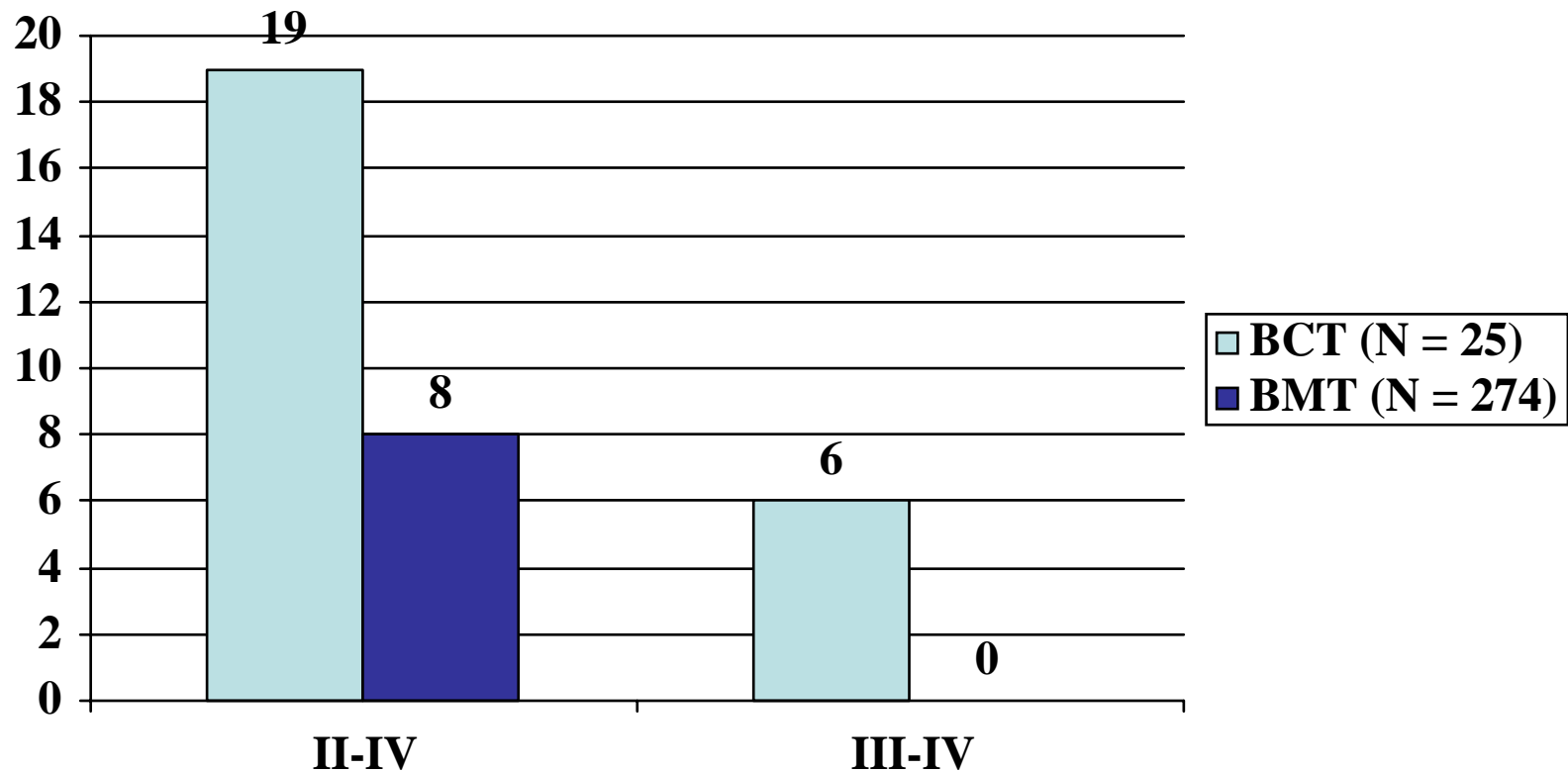
# Do both case-control studies show same effects?

	Calgary in-house	CIBMTR	Explanation of difference
TRM	significant	significant	
Overall mortality	significant (just)	significant	
Acute GVHD	“trend”	significant	Power of study
Chronic GVHD	significant	No difference	Higher in Calgary controls

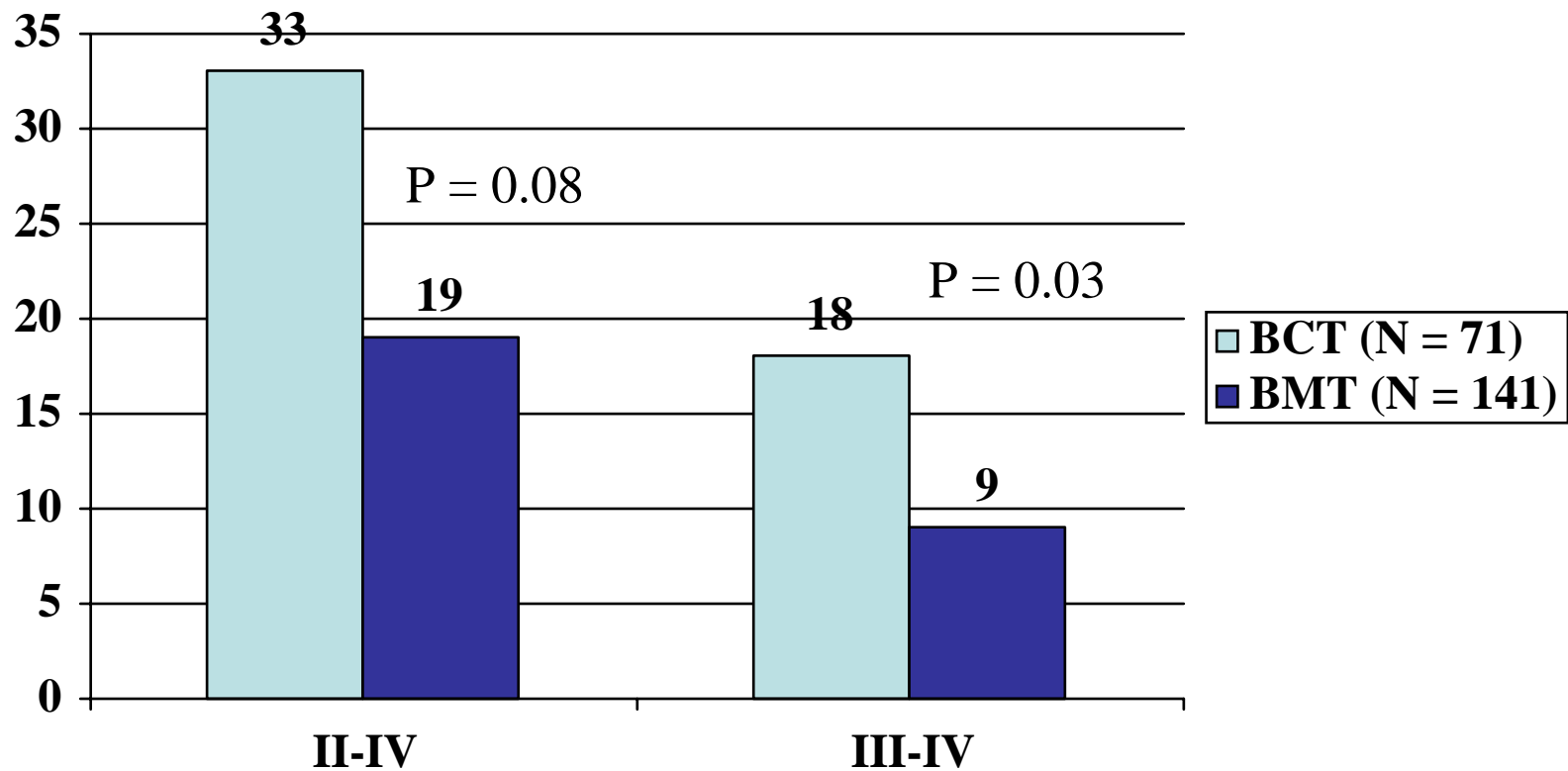
# Effect of cell source on acute GVHD with FLUBUP/ATG



# Acute GVHD-Matched Related Donors Blood Cells vs Bone Marrow FLUBUP



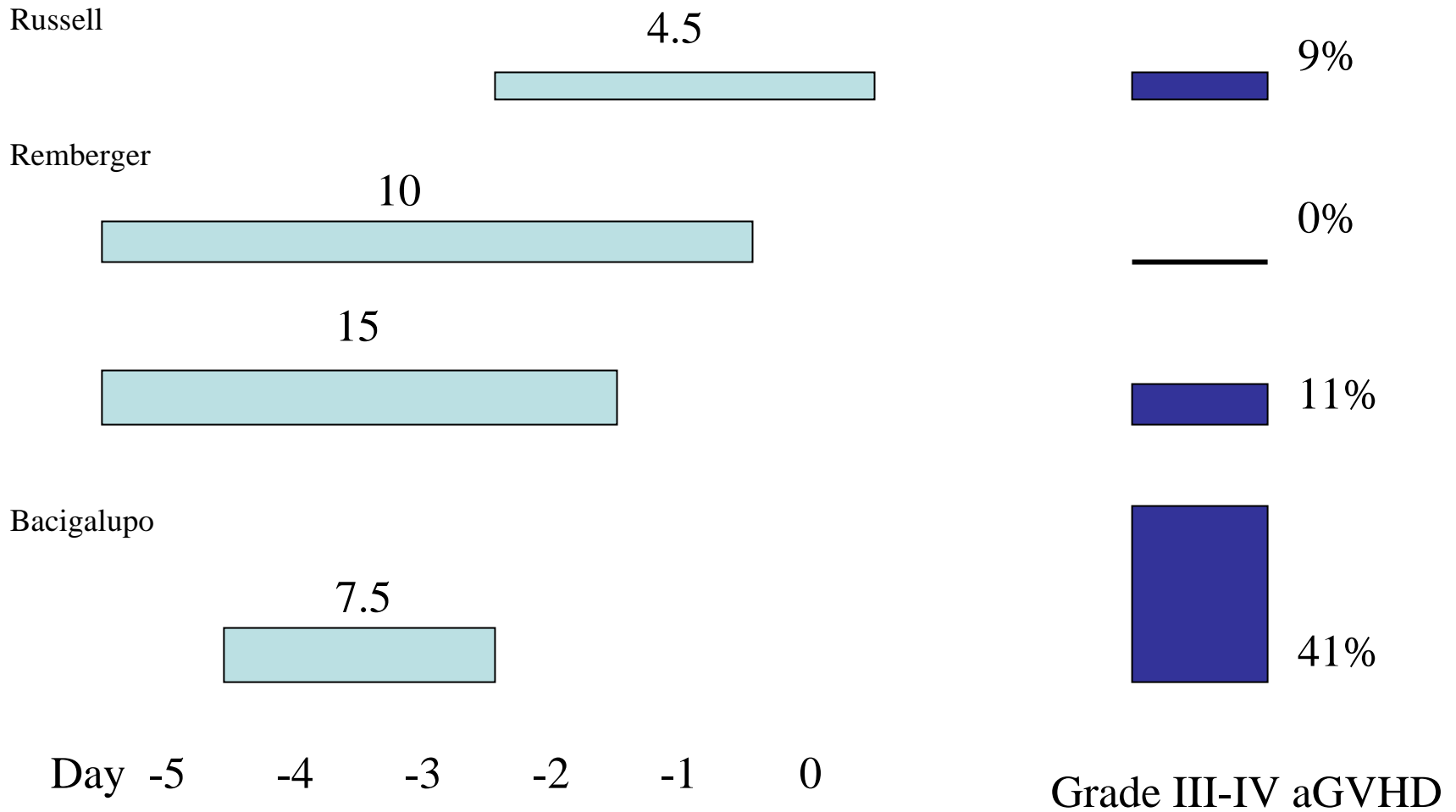
# Acute GVHD-Unrelated Donors Blood Cells vs Bone Marrow FLUBUP



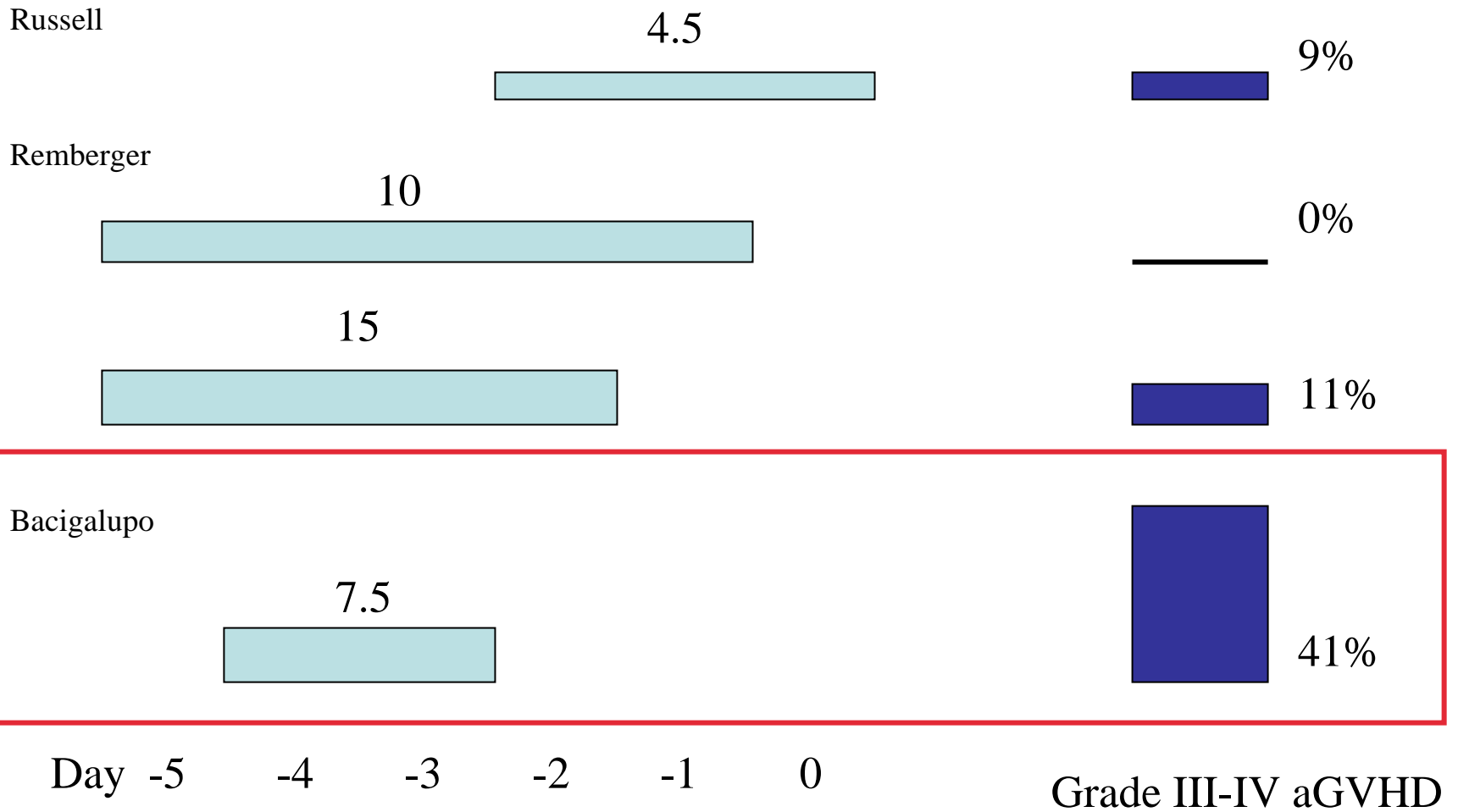
**Does dose and timing of ATG  
matter?**



# Dose and timing of Thymoglobulin before myeloablative BMT from unrelated donors

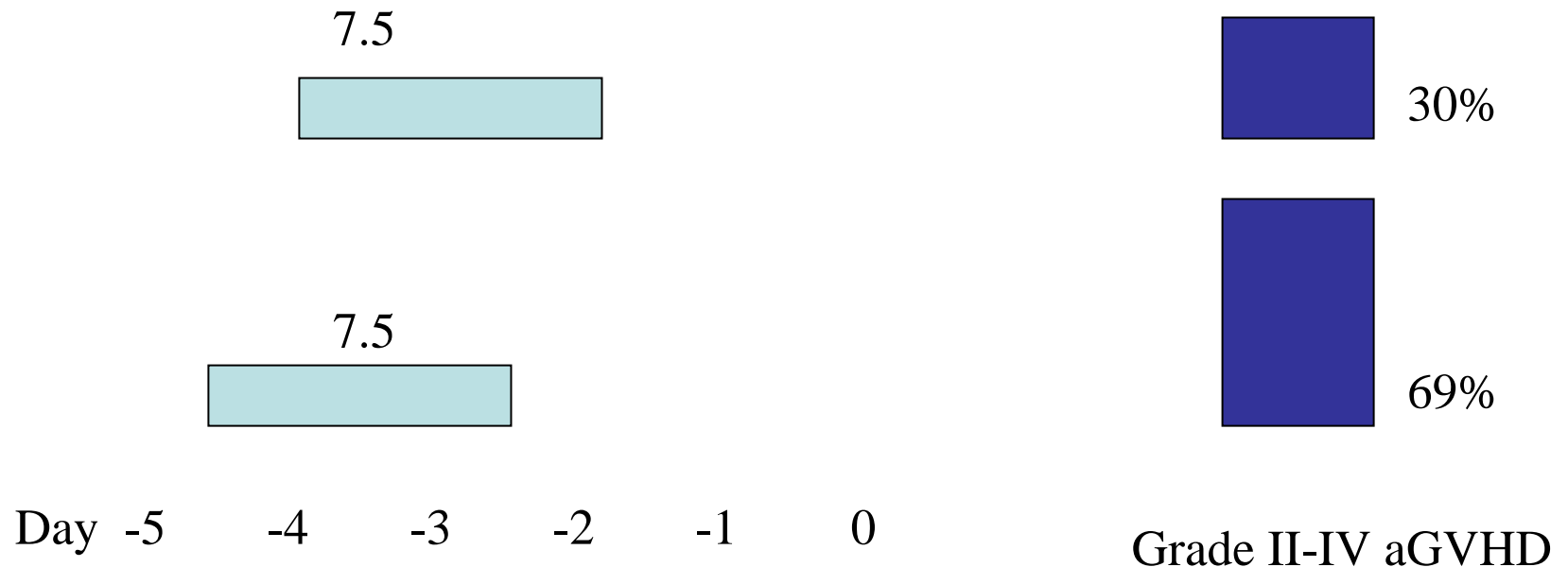


# Dose and timing of Thymoglobulin before myeloablative BMT from unrelated donors

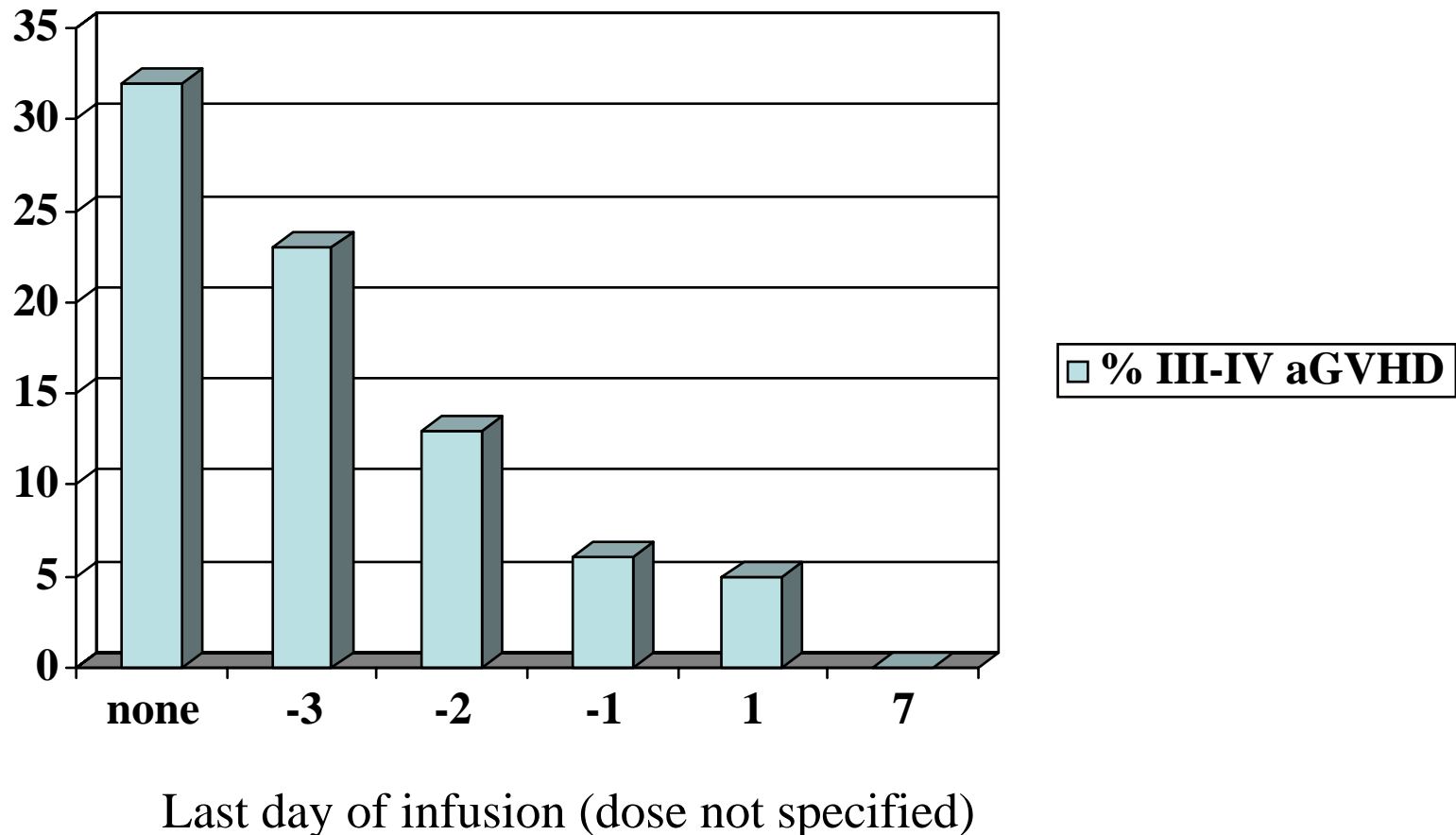


# Dose and timing of Thymoglobulin before myeloablative BMT from unrelated donors

Dominietto et al. Blood 2003(abstr)



# Timing of Thymoglobulin before myeloablative BMT from unrelated donors



# Association of antibody (r-IgG) levels with aGVHD after UD SCT

- In all 128 patients:
- aGVHD associated with:
  - Low r-IgG
  - ATG dose
  - Conventional conditioning
- In AML (53) low levels associated with:
  - More aGVHD
  - Less relapse ( $p = 0.09$ )

# CHALLENGES

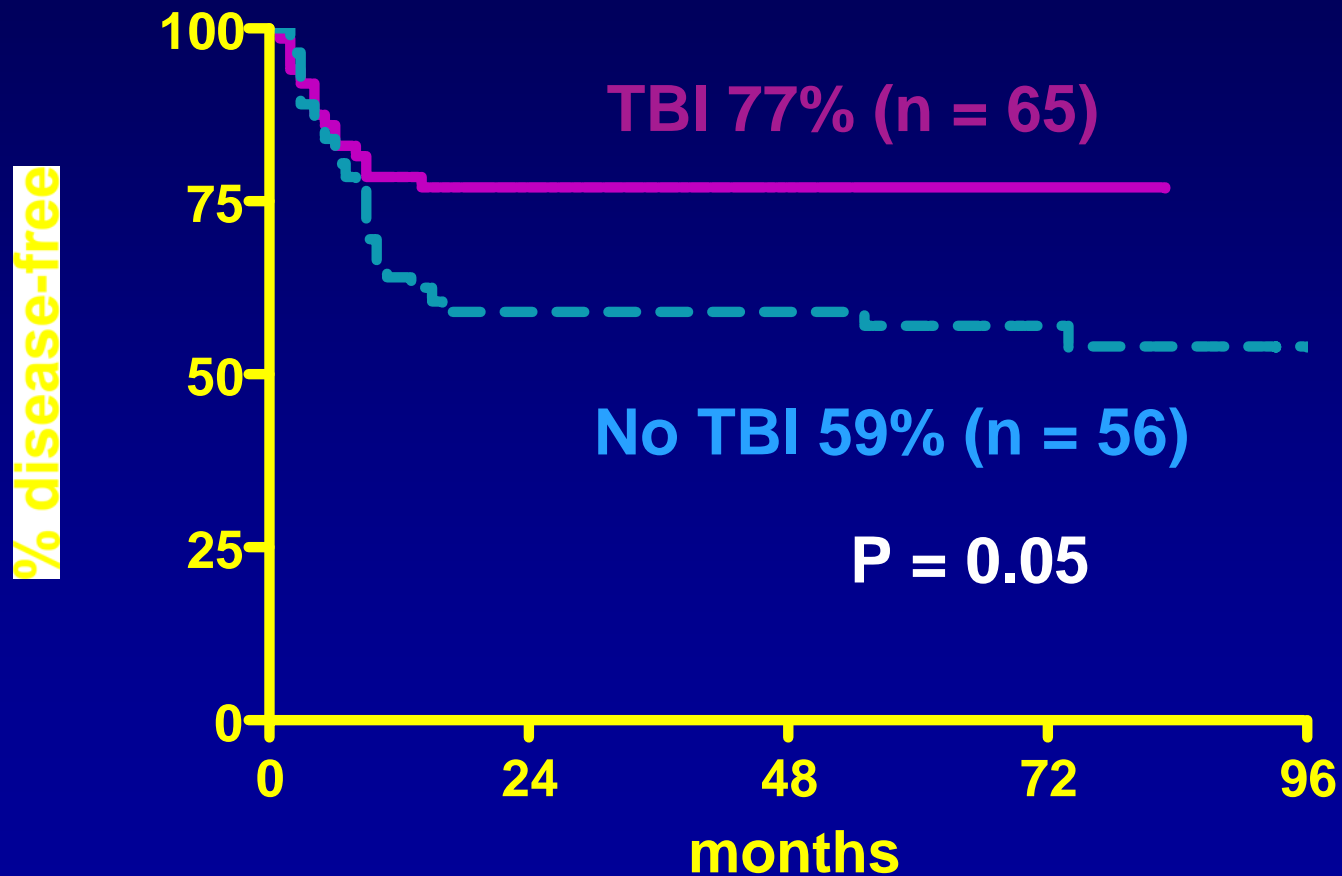


**Can we compensate for the  
trend to more relapse with  
this regimen?**



# DFS AML CR1/CR2 (3 yr)

## Effect of adding TBI to FLUBUP



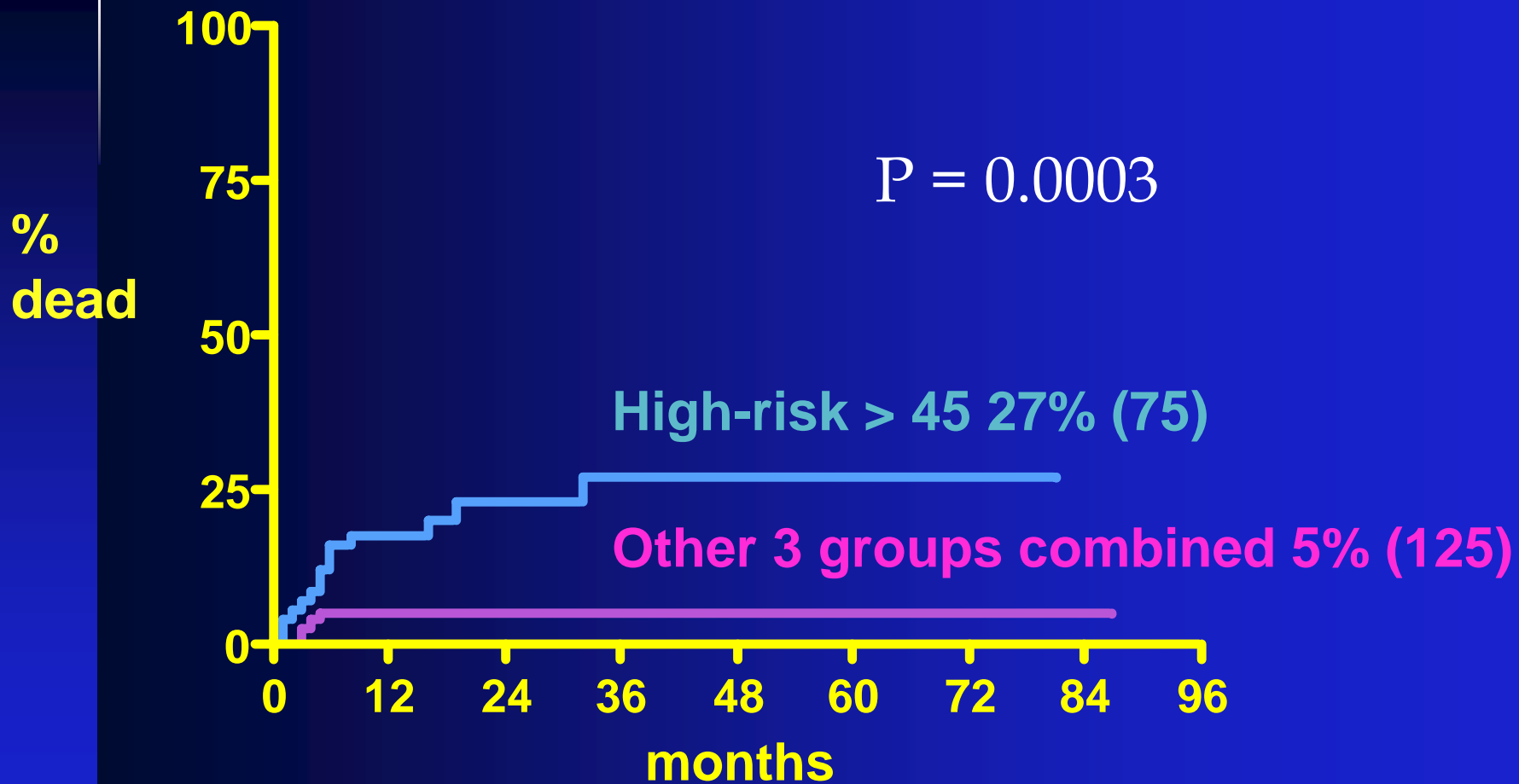
# COX PROPORTIONAL HAZARDS ANALYSIS OF EFFECT OF TBI

	HAZARD RATIO	P
RELAPSE	0.29	0.0001
MORTALITY	0.50	0.009
DFS	0.43	0.001

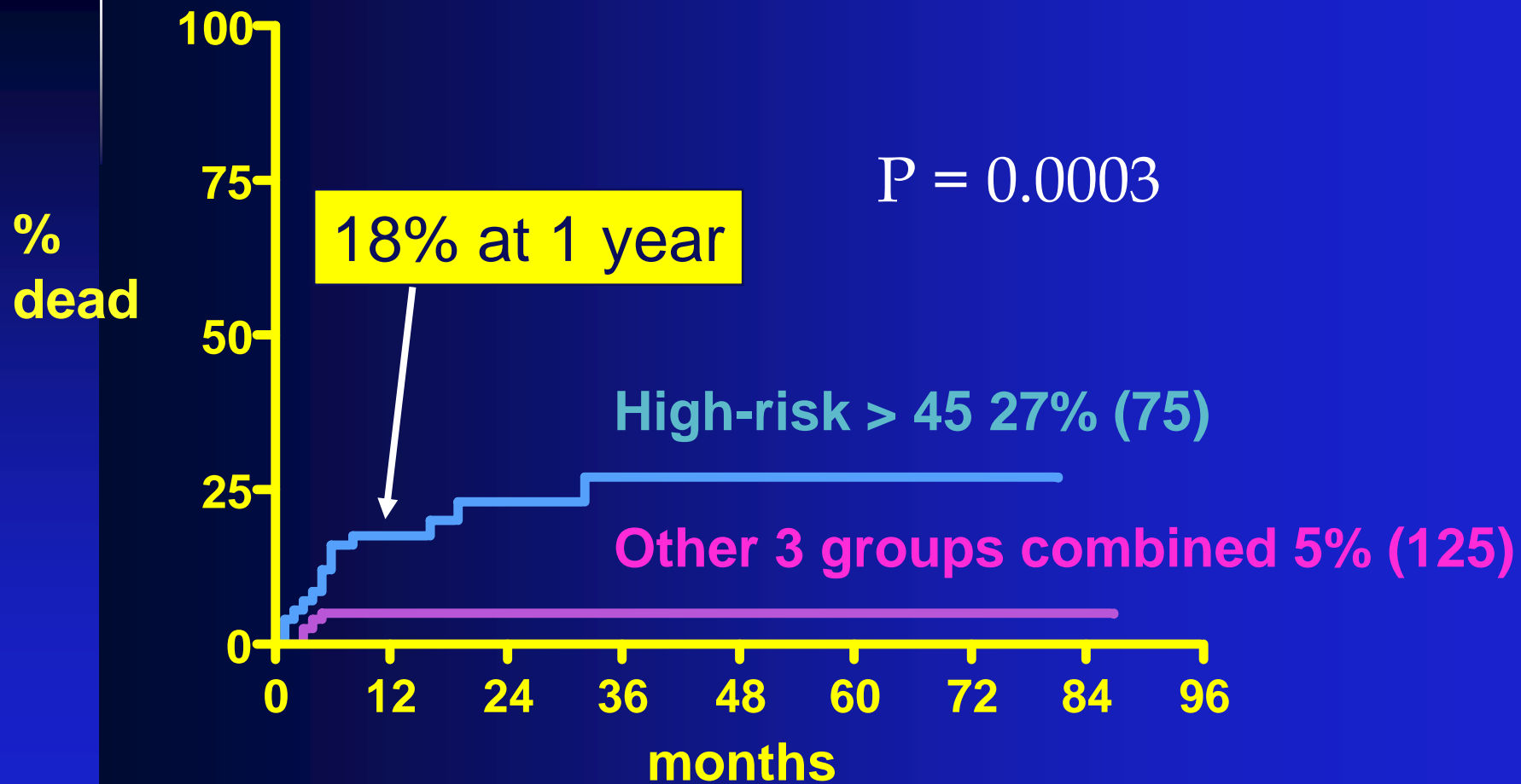
**Can we identify patients at  
high risk of NRM with this  
regimen?**



# TRM after MRD HSCCT



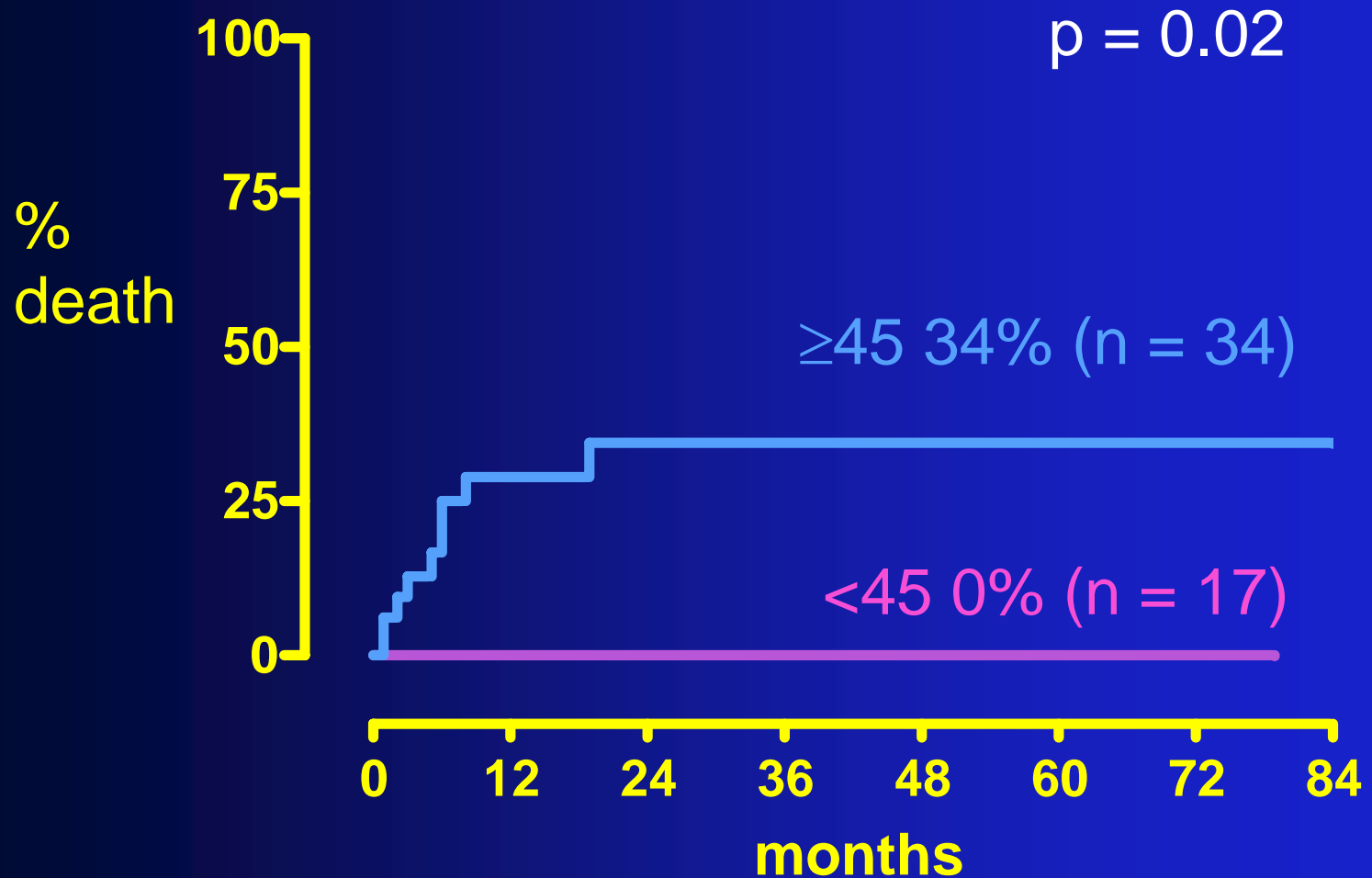
# TRM after MRD HSCCT



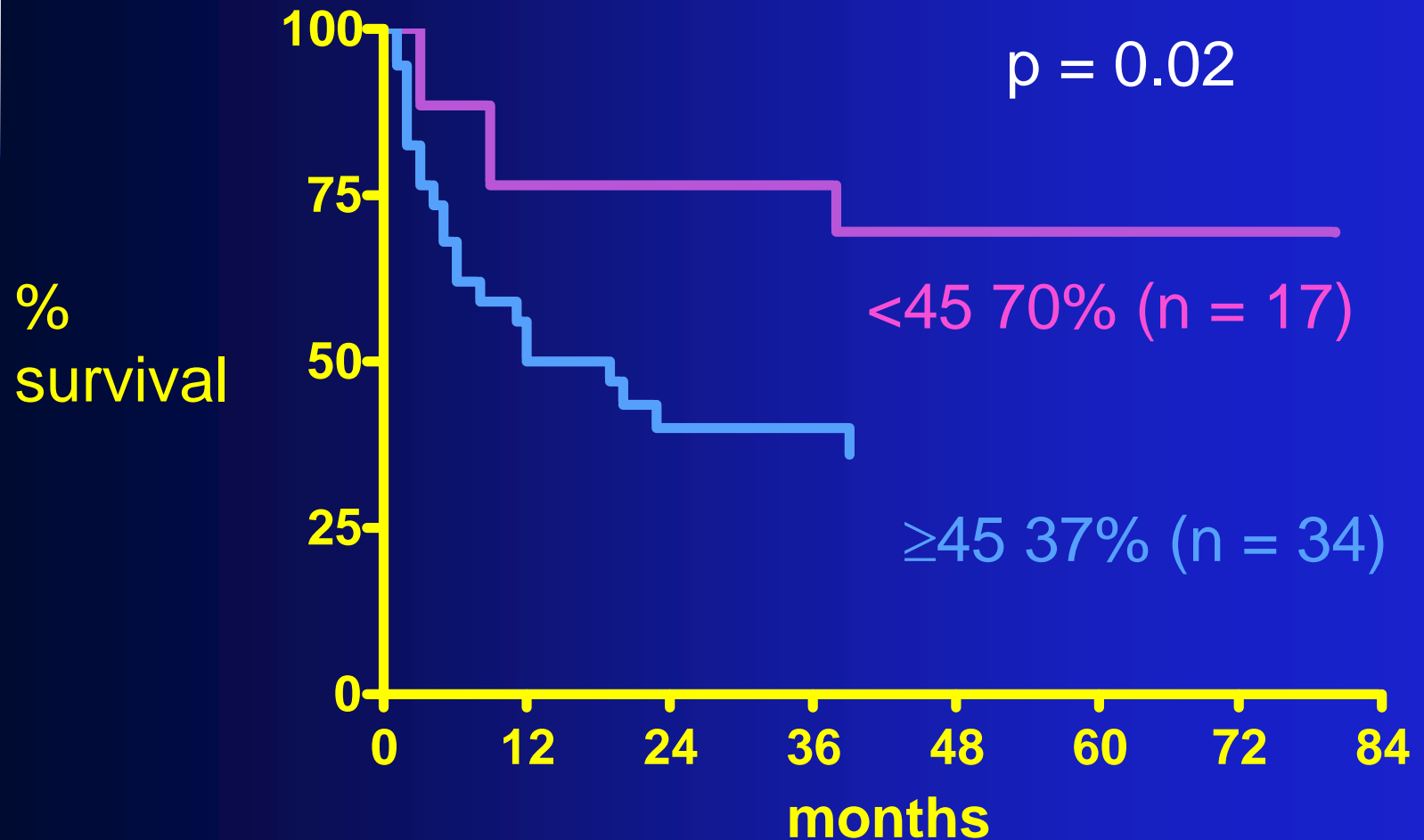
# Why is TRM higher in high-risk older patients?

- Because they have different diseases?
  - e.g more MDS, less HD
- Because they get more GVHD?

# TRM high risk patients, matched pair analysis



# OS high risk patients, matched pair analysis



# GVHD in older high-risk patients vs others

	Older high risk (n = 75)	Others (n = 125)	p
acute GVHD grade II-IV	23%	10%	0.02
acute GVHD grade III-IV	4%	2%	ns
chronic GVHD	66%	41%	0.001
GVHD related death	12%	2%	0.01

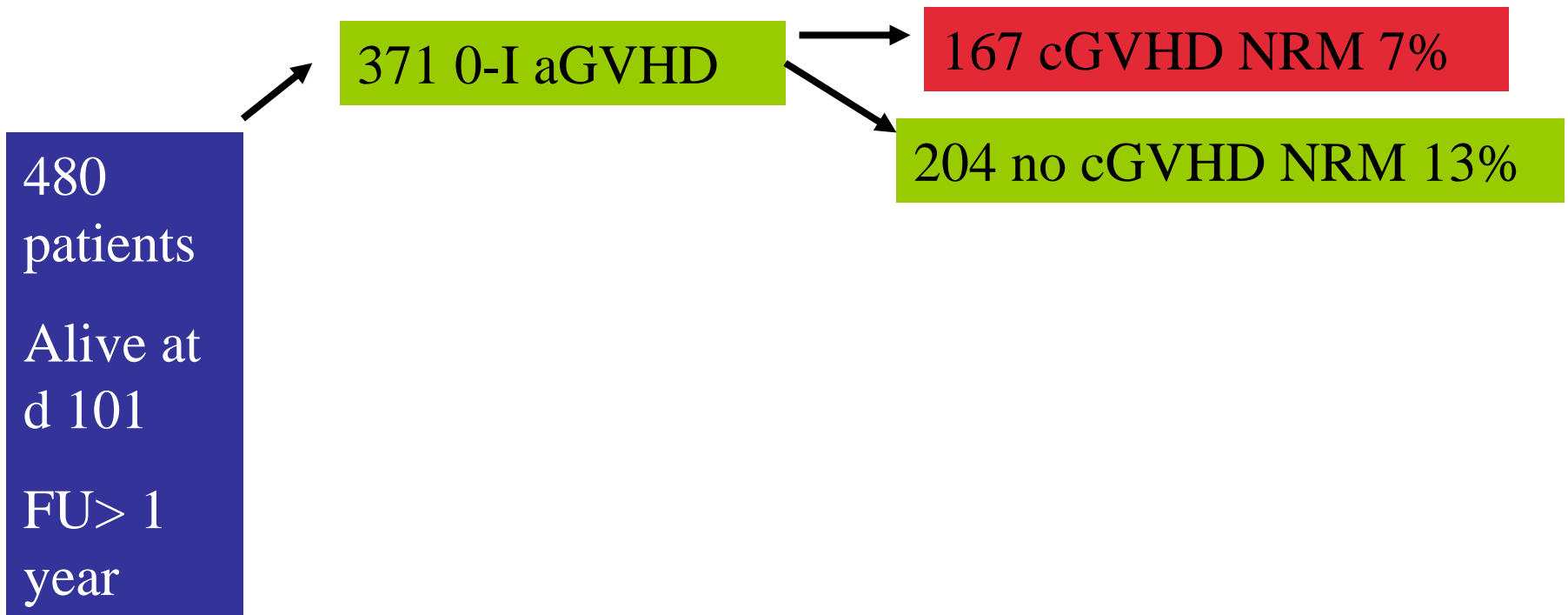
**No acute GVHD is good but  
only bad cGVHD is bad**



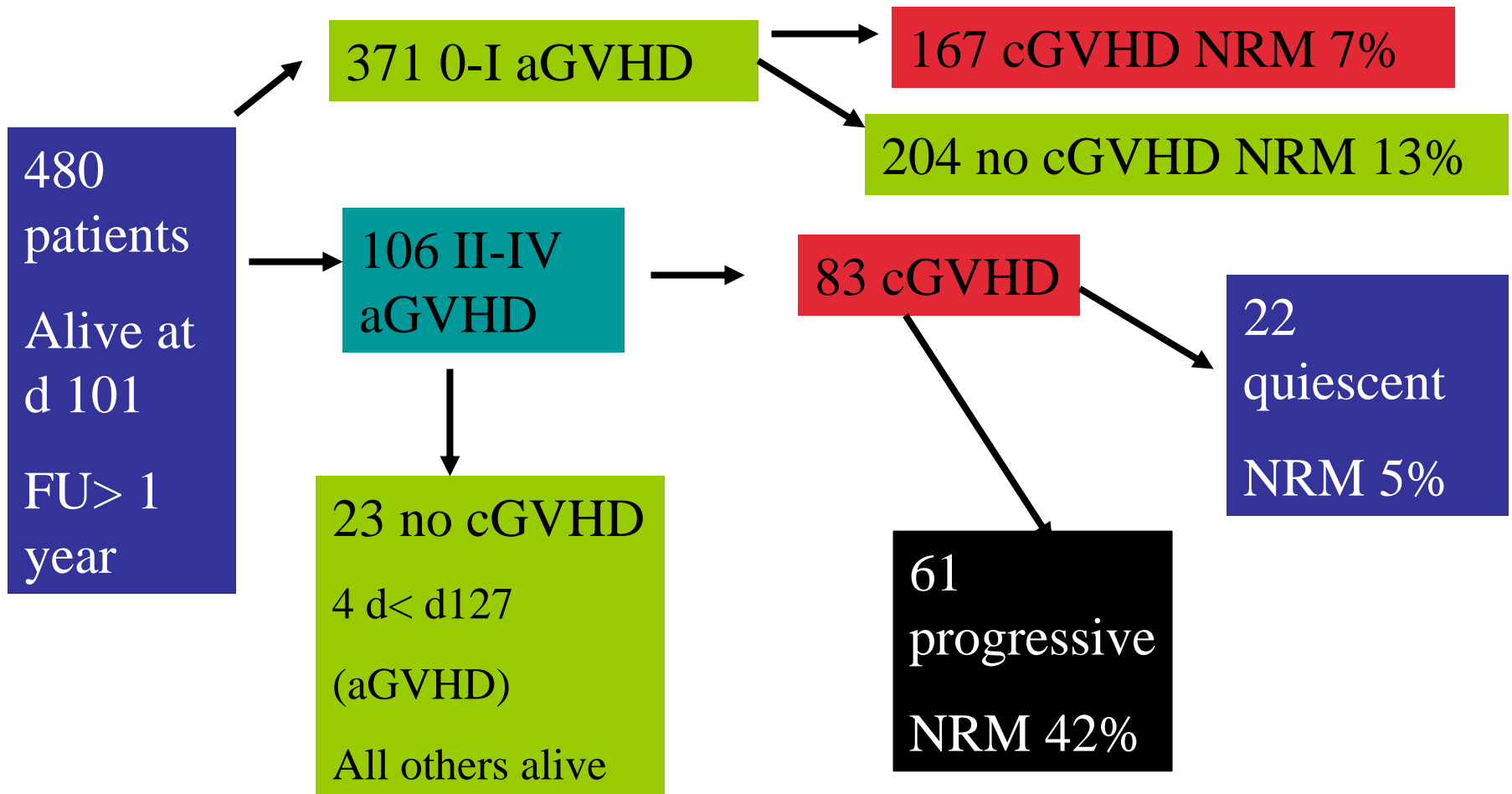
# The importance of preventing acute GVHD - I

aGVHD	0-I (n = 414)	II-IV (n = 124)
D100 NRM (%)	7	12

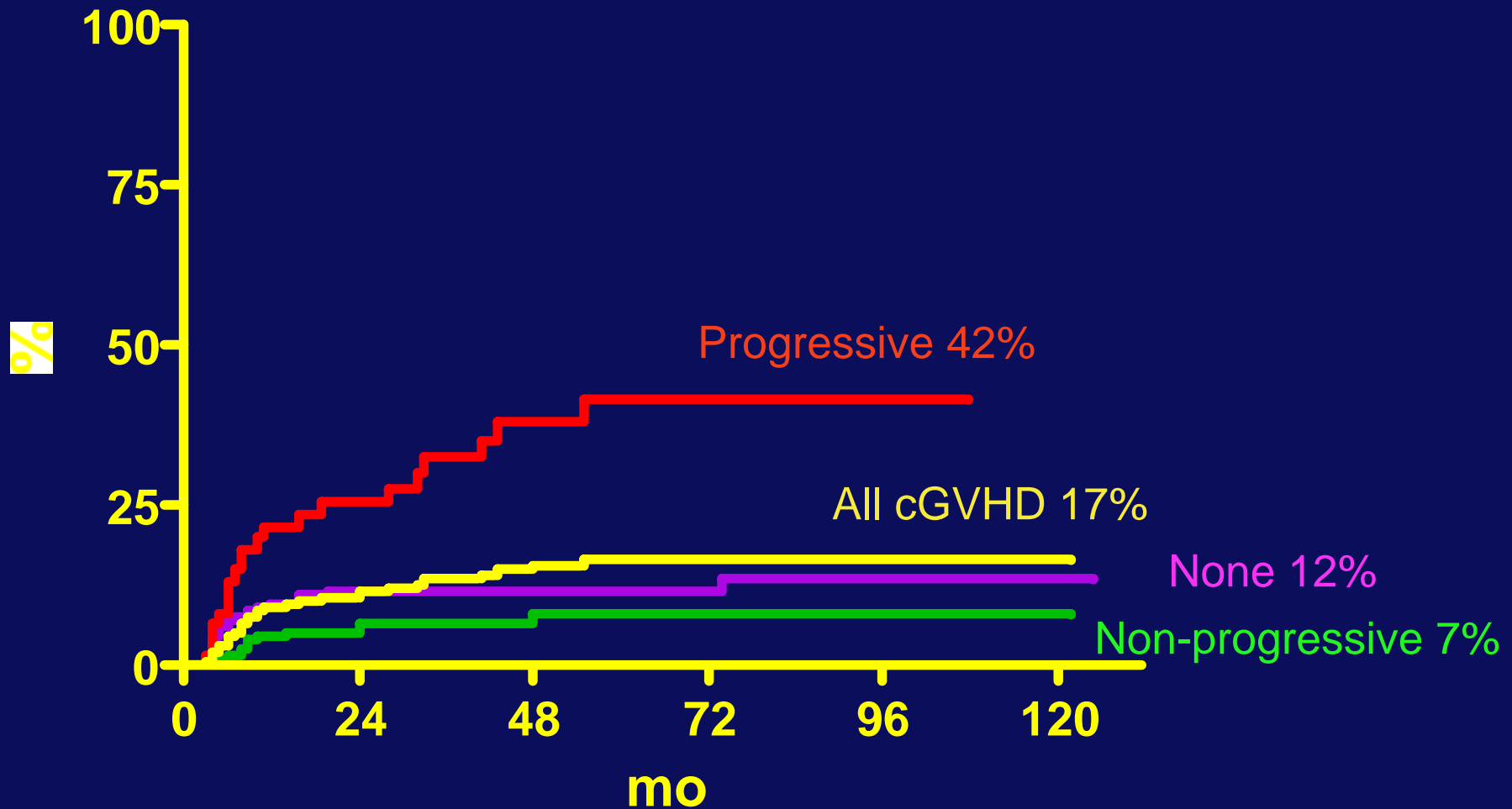
# The importance of preventing acute GVHD - II



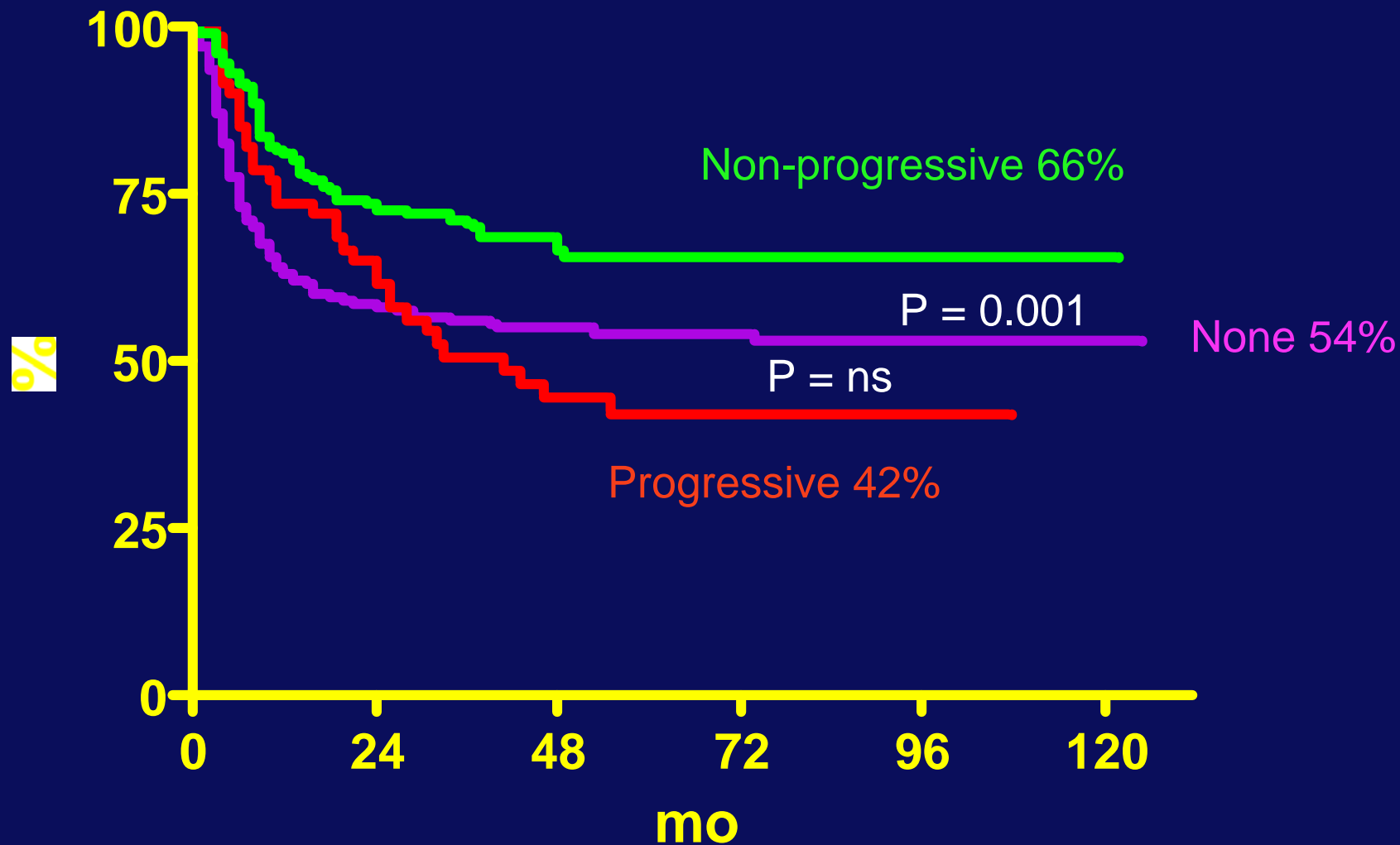
# The importance of preventing acute GVHD - II



# 5yr NRM in 100d survivors by cGVHD



# 5yr DFS in 100d survivors by cGVHD



Toxicity of regimen

Antileukaemic effect of regimen

Relapse



GVHD

GVL

# ACKNOWLEDGEMENTS

## Calgary



- Ahsan Chaudhry
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